ACTA RADIOLOGICA
EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE ET SUECIAE

VOL. 46 DECEMBER 1956 FASC. 6

THE TEMPORAL HORN: ITS DEVELOPMENT, NORMAL VARIATIONS AND CHANGES ASSOCIATED WITH NON-EXPANDING EPILEPTOGENIC LESIONS OF THE TEMPORAL LOBE

by

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Among the cases of focal epilepsy suitable for surgical therapy, a large proportion appear to arise in the region of the temporal lobe. Thus among PENFIELD and KRISTIANSEN's (1951) 222 cases, 95 took origin from the temporal lobe, sylvian region, or these areas and their immediate environs. Our experience in a smaller number of cases supports this evidence.

Tumors are seen in association with chronic focal epilepsy in only a relatively small percentage of cases. This percentage amounted to about 17 % of PENFIELD and KRISTIANSEN's (1951) 222 cases while in the present series, from which expanding lesions (as judged by pneumography) were excluded, tissue of certain neoplastic appearance was encountered but once. By far the most common lesion consists in focal degenerative or cicatricial areas in the brain (PENFIELD and HUMPHREYS 1940; EARLE et coll. 1953) and it is this group in which pneumographic evidence of atrophy may be expected. Although much has been written regarding the association of epilepsy with calcifying lesions of the brain, some at least appearing to be related to small vessel vascular malformations, (GEYELIN and PENFIELD 1929; PENFIELD and WARD 1948; and FALCONER et coll. 1953) these lesions in our experience seem infrequent. Only one was encountered in the present material. In about 13 % of PENFIELD and KRISTIANSEN's cases no pathologic lesion was verified.

Submitted for publication 2 January 1956.

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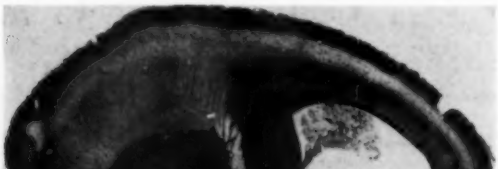

Fig. 1. Foetus 119 mm. Vertico-sagittal section of brain, showing position of amygdala (a), and tail of caudate nucleus (b), as it forms the roof of the temporal horn. Lateral portion of hippocampus is indicated by (c).

This is a somewhat smaller frequency than was seen in our material. However, since the brain samples showing the maximal electrocorticographic abnormality were routinely sent to the neurochemist rather than the neuropathologist our differing results may simply be a matter of sampling.

In attempting to evaluate the pneumograms of patients suffering from epilepsy arising in the region of the temporal lobe, the authors have been able to find little to guide them in the literature with respect to changes associated with atrophic lesions of this area. Indeed little enough has been written of the normal radiographic anatomy of the temporal horn and discussion of its abnormalities has centered nearly exclusively upon the distortions produced by neoplasms.

LINDGREN (1948) had previously emphasized the importance of radiographic views in both the sagittal and lateral projections for evaluation of the temporal horn. The complexity and variability of the structures which define the temporal horn became apparent in our review of normal formalin-fixed brains so we can heartily endorse his advice. By comparing the anatomical material with the radiographs, the interpretation of abnormality was aided and a system of measurements evolved for comparison of case to case. Since the actual tissue loss through atrophy in many epileptogenic lesions is often of minor degree, the usefulness of gas contrast studies in this condition must be expected to be less than with gross expanding lesions of the brain. However, review of the present material has given evidence that the usefulness of pneumography in epileptogenic lesions of the temporal lobe may be enhanced by proper observation.

The development and normal variation in configuration of the temporal horn. In understanding the normal anatomical variations of the temporal horn, inquiry must be made as to the form of structures which define its outline. In the embryo of 11.8 mm (crown-rump length), there appears in the dorsal part of the evaginating hemisphere a slight thickening of the wall itself and a thickening of the medullary velum. These features

were considered by HINES (1922) as the first differentiation of the primordial hippocampus. There is no clear temporal prolongation of the hemisphere in HINES' diagram of the 11.8 mm or 14 mm embryos but in the 19.1 mm embryo a temporal lobe appears. In both the embryos of 19.1 mm and 20 mm the whole length of the hippocampal primordium contains a groove, the fissura hippocampi. The appearance of this groove results in the first vestige of the infolding of the hippocampus (viz. HINES' Fig. 37) and foreshadows the subsequent profound invagination of the hippocampal prominence within the temporal horn.

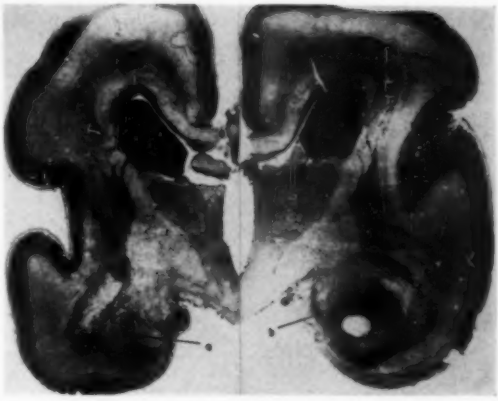

Fig. 2. Foetus 156 mm. Vertico-transverse sections of brain; the one to the left is somewhat anterior to that on the right. Bulk of amygdaloid nucleus (a) lies anterior to tip of temporal horn, but its posterior extension (b) lies on the medial aspect.

If the intervening development may be neglected, and the brain of a 119 mm foetus (16 + weeks) be considered in vertico-sagittal section (Fig. 1), the degree of laminar differentiation of the hippocampus and its striking encroachment upon the lumen of the temporal horn are evident. At this stage, the tail of the caudate nucleus forms the major part of the roof of the ventricle. The amygdaloid nucleus is evident and defines the antero-superior limits of the ventricle. In many adult brains, this nucleus becomes partially engulfed by the anterior migration of the tip of the temporal horn so that it may form a distinct depression in the anterior termination of the ventricle.

Vertico-transverse sections through the brain of a 156 mm foetus (19 + weeks) (Figs. 2 and 3) show the degree of differentiation attained by the temporal horn at this stage. The tail of the caudate nucleus still forms the major portion of the ventricular roof. The amygdaloid nucleus lies above and somewhat medial to the tip of the temporal horn displacing the actual ventricular opening below it. In a foetus of 160 mm (estimated 139 days) BARBÉ (1938) shows a similar state of affairs.

BARBÉ (1938) also provides illustrations of vertico-transverse sections through the brain of a foetus of 220 mm (estimated 167 days). These figures (Fig. 247, p. 202 and Fig. 248, p. 203) show the collateral fissure in the absence of the lateral temporal fissuration and so suggest that it is a more primitive landmark. In our example shown in Fig. 4, although the foetus has an identical crown-rump length (estimated age 25 + weeks) fissuration of the temporal convexity is well established and the collateral fissure produces a vestigial convexity within the temporal horn, the primordium of the collateral eminence.

In the adult, the temporal horn takes origin from the trigone and swings downward, anteriorly and somewhat laterally into the temporal lobe. At a point which may be considered roughly as the junction between the middle and anterior thirds of the temporal horn, the ventricle turns slightly medially to terminate about 2.5 cm from the anteriormost

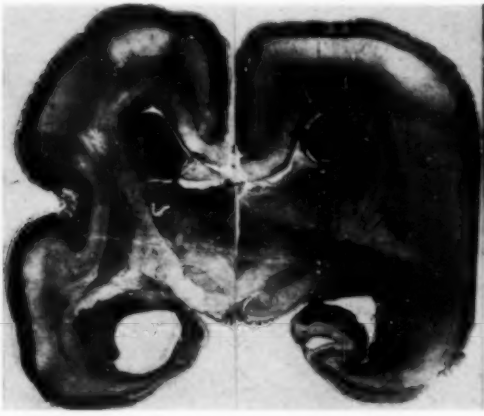

Fig. 3. Foetus 156 mm. Vertico-transverse section of brain taken posterior to the one shown in fig. 2. On the left, the rounded outline of the ventricle anterior to the hippocampus is apparent (this is the area included in measurement E), while in the right the indentation of hippocampus reduces the ventricle to a semilunar outline.

Fig. 4. Foetus 220 mm. Vertico-transverse section of brain showing the collateral fissure (a), and a vestigial collateral eminence (b). Early fissuration on the temporal convexity.

boundary of the temporal lobe. The slightly curved basically tubular outline of this cavity retains its convexity superiorly where the roof of the temporal horn is formed largely by the tapetum of the corpus callosum. Medially, the tail of the caudate nucleus and the optic radiation contribute to this boundary. Between the optic radiation and the ventricle, and medial to the tail of the caudate nucleus, lie the thin stria and taenia semicircularis. Anteriorly, in the roof of the temporal horn, these pass medially to the amygdaloid nucleus so that the optic radiations in this region come to lie directly upon the ventricular ependyma (cf. RILEY 1943, p. 254—274). These structures, however, fail to leave markings gross enough to influence the radiographic outline of the temporal horn.

The medial wall and floor of the ventricle are indented by the hippocampus, reducing it to a semicircular outline with its convexity directed supero-laterally. Posteriorly, this outline of the hippocampus is rounded. Anteriorly, in the temporal horn, it becomes somewhat flattened as the pes of the hippocampus is formed. Frequently the pes hippocampus has a well defined scalloped appearance (the digitations of the pes hippocampi), as may be seen on lateral roentgen films.

The intrusion of the hippocampus within the temporal horn lends it a semilunar outline or, perhaps more properly, may be said to divide

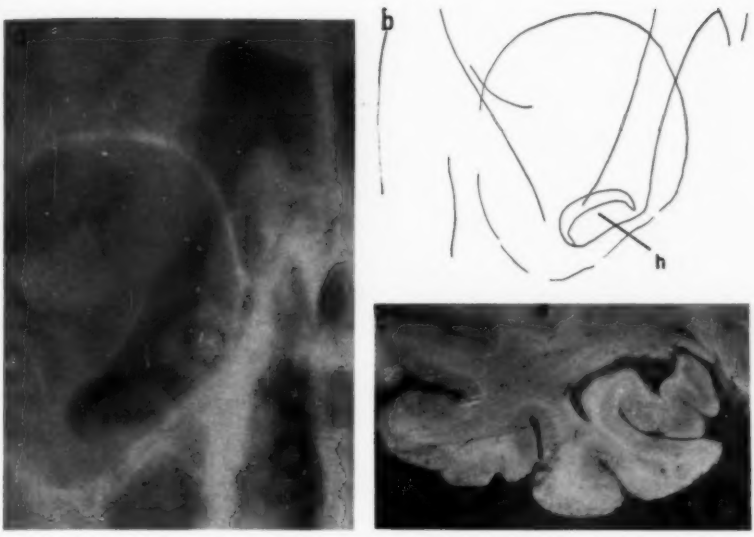

Fig. 5. a) Transorbital sagittal view of temporal horn. b) Tracing of (a). c) Transverse section of brain in anterior half of temporal horn, of similar type as in (a). Neither the collateral fissure nor the third temporal sulcus indent the temporal horn (h, hippocampus).

the temporal horn into one portion superior to, and one portion lateral to the hippocampus. CHILDE and PENFIELD (1937) called these divisions respectively the *supracornual cleft* and *body* of the temporal horn. LINDGREN (1948) objected to the term body as leading to possible confusion with other portions of the ventricular system and substituted the term *lateral cleft* for that portion of the temporal horn lateral to the hippocampus. This nomenclature has been perpetuated in the present discussion.

The lateral floor and the inferior portion of the lateral wall of the temporal horn (*i. e.* below the point at which the tapetum contributes to its outline) are generally said to be formed by the collateral eminence. As it will be recalled, the convexity of the temporal lobe is in general provided with five major convolutions, the first, second and third temporal convolutions, and the fusiform and hippocampal gyri. The collateral fissure is usually defined as the fissure between the hippocampal and fusiform gyri, and the ventricular indentation produced by this fissure is called the collateral eminence. This point is of some importance as it will be noted in Fig. 8 that the third temporal sulcus may produce a profound elevation in the infero-lateral aspect of the temporal horn. Since the resultant ventricular deformity is the same regardless of the

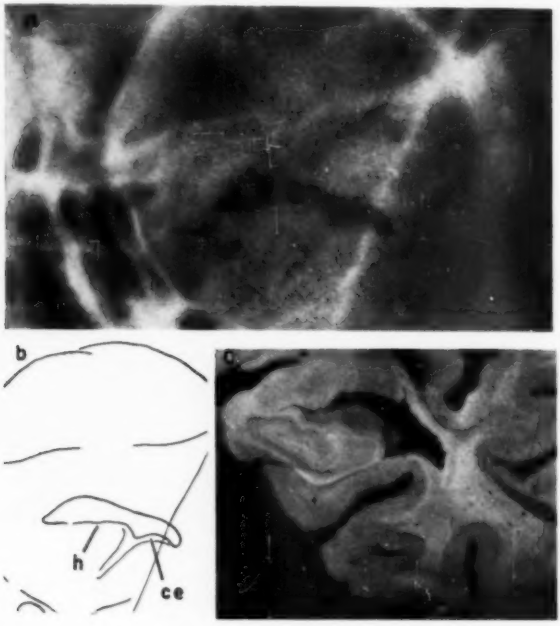

Fig. 6. a) and b) Transorbital sagittal view of temporal horn, the deepest part appearing to lie lateral to the collateral eminence (ce, collateral eminence; h, hippocampus). c) Transverse section of brain in anterior half of temporal horn; the collateral fissure indents medial portion of the horn.

sulcus which produces the indentation, the term collateral eminence is retained in the subsequent discussion though the term "collateral" may obviously not be strictly correct.

Based upon the varying position of the collateral eminence, the four general types of temporal horn as seen in transverse section may be defined as follows.

1) The collateral eminence fails to indent the ventricle. This results in a ventricle of crescentic transverse outline with the hippocampus in its concavity (Fig. 5).

2) The collateral eminence indents the medial portion of the ventricular floor just lateral to the hippocampus. The crescentic outline of the ventricle is maintained but there is a double medial concavity produced by the hippocampus and the collateral eminence (Fig. 6).

3) The collateral eminence may indent the ventricular floor at its lowest point and produce a central elevation, as in Fig. 7.

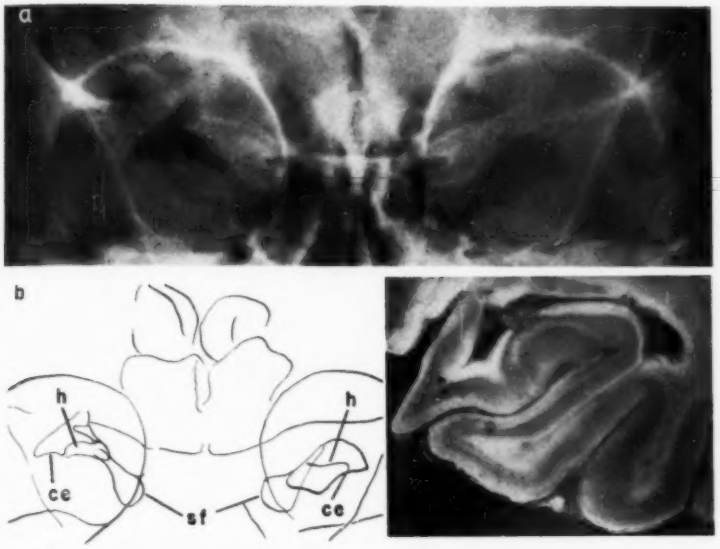

Fig. 7. a) and b) On the left, the temporal horn resembles the anatomical specimen while on the right it resembles the one shown in fig. 8. (ce, collateral eminence; h, hippocampus; sf, superior orbital fissure.) c) Transverse section of brain in anterior half of temporal horn.

4) The collateral eminence (in our cases usually produced by the third temporal sulcus) may indent the infero-lateral angle of the temporal horn (Fig. 8) and produce a roughly 'T'-shaped ventricular outline.

The amygdaloid nucleus may form the third major indentation of the temporal horn. This nucleus, in its posterior portion, lies rather medial and superior to the tip of the temporal horn. Due to its small size at this point it leaves little mark upon the ventricle. From this start it extends anteriorly and rounds the anterior superior aspect of the temporal horn. At this point, or usually somewhat on the antero-superior-lateral portion of the tip of the temporal horn, it attains its maximal size and ability to indent the temporal tip.

On the lateral views of the temporal horn, the superior outline of the tip is seen to bend downward, forming at this point the *genu* of the temporal horn (Fig. 12) and leading in most instances to the fact that the most anterior portion of the temporal horn is also its most inferior portion.

One further variation of normal consists in the adherence of the lateral aspect of the hippocampus to the adjacent wall of the temporal horn, thus anatomically separating the supracorneal from the lateral clefts.

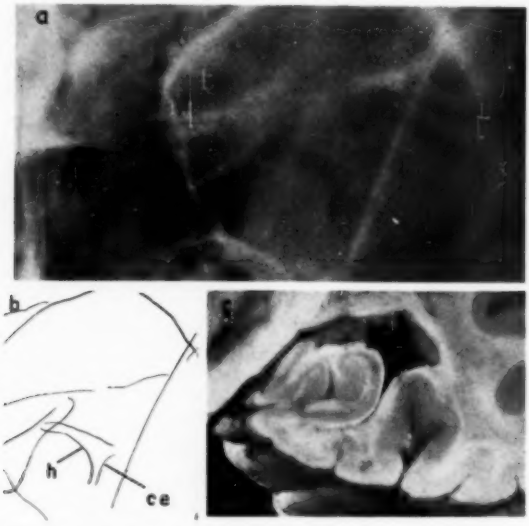

Fig. 8. a) and b) Transorbital view of temporal horn (ce, collateral eminence; h, hippocampus). c) Transverse section of brain in anterior half of temporal horn, the collateral eminence indenting lateral portion of its floor.

CHILDE and PENFIELD (1937) illustrate such a case, LINDGREN (1948) included three further examples, and a similar instance appears in Fig. 9. BATES and NETSKY (1955) have more recently discussed these variations. In all instances including the present one, this band of tissue was present in only the anterior portion of the temporal horn. It may be noted, however, that in this case and in another in our collection, this adherence between the hippocampus and the ventricular wall appeared only upon the lateral aspect of the hippocampus, leaving its anteriormost portion quite free.

As will be appreciated from inspection of Fig. 7, the configuration of the temporal horn in transverse section may differ on the two sides.

TORKILDSEN (1933—34), in 11 ventricular casts of normal brains, found that the length of the temporal horns might vary from 2.5 to 5.0 cm and the length in the same specimen of the two temporal horns might differ by as much as 0.8 cm. In gas contrast studies considered normal he found that the length of the temporal horns might differ in the same patient by as much as 1.7 cm as measured on the film. In these same individuals the total height of the temporal horn, as seen on the lateral view and measured at the ventricular tip, might differ as much as 0.6 cm from one to the other side. It may not be out of place, however, to point out that some of the patients providing the 'normal' encephalograms

suffered from epilepsy. Small consideration was given to epilepsy of the temporal region at the time of his writing.

The mechanism of dilatation of the temporal horn. Very little attention has been paid to the specific changes manifest in the temporal lobe in disease of the nervous system. TORKILDSEN and PIRIE (1934), CHILDE and PENFIELD (1937), and LINDGREN (1948) have noted the pneumographic results of tumors of the temporal lobe.

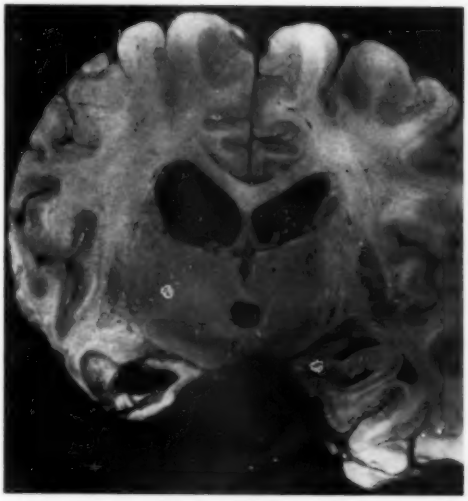

Fig. 9. Illustration of effect of tissue loss in anterior temporal region upon outline of temporal horn (temporal lobectomy performed 45 days before death). Ipsilateral dilatation of body of ventricle; adherence between hippocampus and lateral wall of horn, anatomically separating the lateral from the supracornual cleft (to the right).

Although it would appear that the study of atrophic cerebral lesions by gas contrast methods has never received extended consideration in the literature, papers on the subject appeared early. DANDY (1923) apparently was the first to report that following brain destruction there might be either focal or general ventricular dilatation. FOERSTER (1924) soon after reported a "wandering" of the ventricular system toward the site of an old brain injury and with PENFIELD (1930) elaborated the thesis of the contracting cerebral cicatrix as a cause for local ventricular deformity.

Thus they contended that brain wounds cause focal ventricular dilatation not only by local loss of cerebral substance but by a dynamic pull upon brain substance, and thereby the ventricular outline, from an outwardly contracting meningocerebral cicatrix. Displacement of the third and lateral ventricles toward an atrophic cerebral lesion was again emphasized by DYKE et coll. (1933) and ROBERTSON and CHILDE (1940) along with the concomitant skull changes (hypertrophy of skull and sinuses and loss of skull curvature over the affected cerebrum). In their examination of the subject, these authors found that shift of the midline toward an atrophic lesion not necessarily indicates the presence of a contracting meningocerebral scar anchored upon the dura. Furthermore, shift of midline structures might be nullified by fluid collections over the local area of atrophy. However, cerebral adhesions may accentuate a ventric-

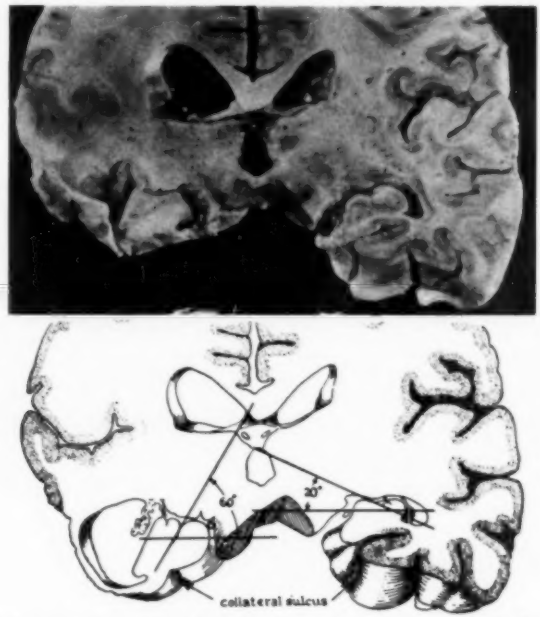

Fig. 10. Section from same case as in fig. 9, taken 1 cm more posteriorly. Plane of hippocampal fissure indicated by the line in the diagram below. This plane is rotated counterclockwise on a sagittal axis, as compared with the position of the homologous hippocampal fissure on the opposite side. The ventricular prominence of hippocampus is nearly lost, increasing even further the width of the lateral cleft.

ular shift toward an atrophic lesion by preventing such a local fluid accumulation.

McRae (1948) reported a series of cases of epilepsy due to non-expanding cerebral lesions. He re-emphasized many of the features mentioned above but apparently paid little attention to the temporal horns apart from warning of their variability and the fact that at times only the supracornual cleft might fill. Apparently, temporal horn evaluation was made from lateral stereoscopic views alone.

We have been unable to obtain for anatomic examination the brain of a patient who, premortem, had suffered from temporal lobe epilepsy in a clinical state comparable to that of patients selected for study in this series. However, Fig. 9 shows the degree of dilatation resulting from anterior resection of the temporal lobe required in the exposure of a meningioma of the middle fossa 45 days before death from pneumonia. (This brain was kindly sent to us by Dr. Francis O'Brien.) Posteriorly, the change in the plane of orientation of the hippocampal fissure is

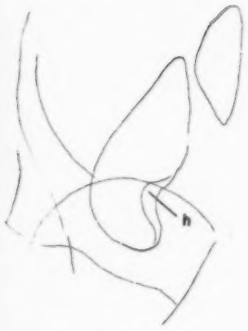

Fig. 11. Pneumography. Gross dilatation of temporal horn in a patient with progressive dementia and seizures, without evident expanding lesion. Hippocampus (h) no longer forms portion of floor of temporal horn.

evident (Fig. 10). The fissure and the hippocampus itself have rotated, counterclockwise, as the ventricle expanded.

This rotating movement of the hippocampus is apparently a common result of dilatation of the temporal horn and may be seen as well in enlarged temporal horns resulting from blockage of the cerebrospinal fluid pathways at the third ventricle or below. Thus the indentation of the hippocampus is lost in a major dilatation of the temporal horn, and this explains the tendency of the horn to approach a circle in transverse outline as dilatation continues (Fig. 11).

It has been possible to repeat the gas contrast studies in two instances following temporal lobectomy. The changes found in the temporal horn appeared similar to those illustrated in Figs. 9 and 10.

Present case material

The cases included in the present study were all instances in which epilepsy was considered to arise in the region of the temporal lobe and in which surgical treatment of the seizures was carried out by one of us (M. B.). The decision for surgical treatment of epilepsy was based primarily upon evaluation of the following evidence: 1) the description of the patient's aura and seizures, 2) the neurological findings, 3) the findings at electroencephalography, 4) the findings on conventional skull films and at pneumography, 5) the failure of control of seizures by adequate and prolonged medical therapy, 6) the degree of disability the seizures

occasioned the patient. In all cases at operation, confirmation of the localization of the seizure origin was obtained by electrocorticography, and usually by either the appearance of macroscopic abnormality of the cerebral substance itself, or reproduction of the patient's attack pattern by cortical stimulation, or both.

All cases of temporal lobe epilepsy operated upon, in which there was evidence sufficient for cortical excision, have been included, except those due to an expanding lesion.

The present method of head positioning for encephalography, which was designed to obtain maximum visualization of the temporal horns, has been the result of considerable trial and error which has extended through the major portion of the period in which the cases reported here were studied.

The following procedure is now in use for demonstration of the temporal horns. After injection of oxygen through a lumbar puncture, the patient is placed in lateral position, and the crown of the head is lowered 10° to aid in gas-fluid displacement in the temporal horn. This degree of lowering of the crown has a further advantage in tending to project the temporal horn above confusing bony structures, particularly those of the mastoid cells. Finally the head is rotated 20° face-up from the horizontal to compensate for the medial curvature of the temporal tip, and lateral stereoscopic views are taken in this position. By appropriately tilting both the tube and cassette a true lateral view is obtained. By repositioning the tube and cassette for an antero-posterior view and extending the head slightly, so that the central ray is approximately 30° below the cantho-meatal line, the transverse outline of the temporal horn may be projected through the center of the orbit. The head is then rotated to the opposite side, the above manœuvres are repeated and similar views taken to outline the opposite temporal horn. Finally the head is returned to a brow-up position, the oxygen distribution equalized in the two ventricles by gentle movements of the head from side to side, then with the patient's shoulders overhanging the head of the stretcher a bit, the patient's neck is extended as fully as possible to displace the oxygen along the floor of the ventricles posteriorly and into the temporal horns. Then the head is brought to a brow-up position modified as given above for projection of the temporal tip through the orbits.

In many instances the patient was returned for films 24 hours after the injection of oxygen. Not infrequently, structures not apparent on the initial films have been outlined, and the reduction of subarachnoid gas tends to result in better definition of the ventricles.

The positioning as given above was originally suggested by TORKILDSEN and PIRIE (1934) (who however, recommended a 30° face-up position) but was discarded by LINDGREN (1948).

LINDGREN used four projections for the examination of the temporal horn, one of them being a transorbital sagittal projection and, perhaps wisely, he refrained from including any angle for head positioning in this projection, remarking that the position of the temporal horn varied with the skull type (cf. BAILEY 1936). Although this would appear true, the 30° angulation below the cantho-meatal line will give in most instances a satisfactory projection and may serve as a general guide.

For evaluation of the present data, careful tracings were made of all portions of the temporal horns visualized in each instance, and from these

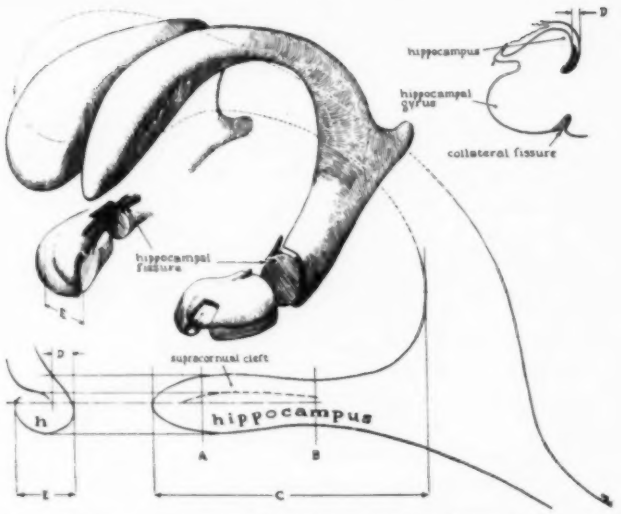

Fig. 12. Diagram of the areas measured on the sagittal and lateral views of the temporal horn.

the measurements were made. The areas measured in the sagittal and lateral projection are as given in Fig. 12.

It will be noted that the total length of the temporal horn C was defined as the distance from the tip to a point on its longitudinal axis from which a perpendicular might be erected to touch the anterior wall of the trigone. Two additional points for measurement were selected in a plane perpendicular to the longitudinal axis. A is at the level of the genu of the temporal horn, while B lies at a point midway between A and the posterior limits of the temporal horn as described above. At both levels, when there is adequate filling, the supracornual cleft and the total height of the lateral cleft may be measured. On the sagittal views, measurement D was taken as the minimum distance from the hippocampus to the lateral wall (*i. e.* the width of the lateral cleft), and the horizontal level at which the measurement was to be taken was arbitrarily set as the apex of the lateral curve of the temporal horn, as seen on this view. Measurement E is the transverse diameter of the temporal horn anterior to the hippocampus. As interpreted in this manner this measurement will vary with the degree of dilatation of the temporal horn. If the closeness of the anterior tip of the temporal horn to the pes hippocampus is sufficient to preclude visible filling of the tip on the sagittal view, no measurement can be made.

Results of radiographic review of the present 41 cases of temporal lobe epilepsy

As in any clinical study, the determination of the 'normal' and the significance of a given deviation from this 'normal' were the most vexing problems. In making paraffin casts of the ventricles of apparently normal formalin-fixed brains, it became apparent that the casts of the temporal horns having the most pleasing appearance were those in which sufficient space was present in the horn to permit the free entrance of the casting medium. Horns having close approximation of the hippocampus and the lateral wall did not permit a satisfactory cast. In the latter instance, there is certainly nothing to suggest that these small temporal horns are abnormal, and in the specimens reviewed for the present study they seemed in numerical predominance. Therefore, suspicion has arisen as to the normality of a number of the commonly pictured ventricular models. Ventricular measurements from "normal" encephalograms of patients with complaints referable to the central nervous system are obviously open to question. The direct answer, consisting in the pneumographic study of healthy persons, would seem beyond approach in good conscience.

Thus, in the present study of 41 consecutive cases, the question of the limits of normal has been avoided. The position has been taken that the combined clinical, electroencephalographic and surgical evidence of the origin of seizure activity forms an adequate basis for localization of the epileptic process. Therefore, arbitrary measurements were tested against the data obtained from the films, in an effort to find those measurements which when applied impartially to all studies would give the highest percentage of correspondence with the above mentioned evidence. It can be hoped that larger series in the future may confirm or improve these criteria.

On this basis, the following measurements were selected as indicating abnormality: 1) over 3 mm difference in the height of the lateral cleft of the two temporal horns at levels A and/or B; 2) over 4 mm total width of the lateral cleft (D). This was taken as an absolute figure and was not used in comparison of one side to the other. When both sides exceeded this figure the larger was selected.

Of the 41 cases, 13 were considered to have insufficient gas filling of the temporal horns for evaluation. Of the remaining 28 cases, 12 (43 %) had no evident signs for localization of the lesion by these criteria, 13 (46 %) were correctly and 3 (11 %) incorrectly localized.

Acknowledgements

The authors wish to acknowledge the kindness of Dr. G. W. Bartelmez of the Department of Embryology of the Carnegie Institution of Washington in permitting a review of their collection and the use of three specimens for illustrations 1—4. Mr. W. Loechel prepared the drawings and Mr. R. Grill and Mr. F. Meiller assisted with the photographic work.

SUMMARY

There is an apparent lack of previous detailed studies of the effect of non-expanding epileptogenic lesions of the temporal lobe upon the outline of the temporal horn as seen at pneumography. The embryonic and adult anatomy of the structures defining the outline of the temporal horn are reviewed. Four normal types are evident on sagittal projections of the temporal horn, depending upon the prominence and position of the collateral eminence. The mechanism of enlargement of the temporal horn is discussed including the factor of displacement and rotation of the hippocampus. In 28 cases, evaluation was possible, and it seems probable that with increasing experience additional information of localizing value may be obtained.

ZUSAMMENFASSUNG

Es besteht ein offenbarer Mangel an früheren eingehenden Studien über die encephalographischen Veränderungen des Temporalhornes bei nicht-expansiver Temporallappenepilepsie. Die anatomischen Verhältnisse des Temporalhornes am Embryo und Erwachsenen werden besprochen. Die Verfasser unterscheiden am Encephalogram 4 normale Typen des Temporalhornes in der sagittalen Projektion, abhängig von der Prominenz und Lage der Emminentia collateralis. Der Mechanismus der Vergrösserung des Temporalhornes wird besprochen, einschliesslich der Verschiebung und Verdrehung des Hippocampus. In 28 Fällen war eine Auswertung möglich, und es ist wahrscheinlich dass mit zunehmender Erfahrung weitere Kenntnisse über den Wert der encephalographischen Seitenlokalisation bei Temporallappenepilepsie erhalten werden können.

RÉSUMÉ

L'effet des lésions épileptogènes non tumorales du lobe temporal sur l'aspect pneumographique de la corne temporale paraît ne pas avoir été étudié en détail jusqu'à maintenant. Les auteurs rappellent l'anatomie embryonnaire et adulte des formations qui délimitent le contour de la corne temporale. Sur l'incidence de face, quatre types normaux sont évidents, dépendant de la saillie et de la situation de l'éminence collatérale. Les auteurs étudient le mécanisme de l'augmentation de volume de la corne temporale, y compris le facteur de déplacement et de rotation de l'hippocampe. En 28 cas, les cornes temporales étaient suffisamment visualisées pour être étudiées et il est probable qu'une plus grande expérience permettra d'obtenir d'autres données pour la localisation.

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CHOLECYSTOGRAPHY WITH THE SODIUM SALT OF IOPANOIC ACID

by

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Since 1951 preparations of 3-(3-amino-2,4,6-triiodophenyl) 2-ethyl propionic acid = iopanoic acid (Telepaque, Teletrast, Bilijodon etc.) have gradually supplanted other types of contrast medium for oral cholecystography. It is generally agreed that this substance gives a better and more frequent filling of the gallbladder than those employed earlier. It is also said to be less toxic and to be accompanied less frequently by side-effects.

It is known that contrast remnants are liable to persist in the digestive tract after examinations with iopanoic acid. SEEDORF & POWELL (1955) wrote: "It has the disadvantage, however, of producing opacities in the intestine, which may be confused with shadows from calcification within the abdomen". According to WHITEHOUSE & MARTIN (1955), of 500 patients receiving 2 g Telepaque 487, or 97.4 per cent, had residues of contrast medium in the colon. Some authors claim that the residues are a consequence of too large a dose. This assumption, however, seems to be wrong. The occurrence of contrast rests may be explained in the following way. The solubility of iopanoic acid, which is a tri-iodized acid, is extremely low. Even if the acid incorporated in the tablets is pulverized, the surface area per unit of weight is small and dissolution of the substance in the intestine therefore relatively slow. The rate of absorption varies with that of dissolution and undissolved contrast medium may persist in the intestine.

In an attempt to overcome this disadvantage the acid was replaced by its sodium salt (Research Departement, A/B LEO, Sweden). The sodium salt reacts completely or partly with the hydrochloric acid in

Submitted for publication 26 June 1956.

the stomach, causing precipitation of the free acid in an amorphous form. The surface area per unit of weight of the acid in an amorphous form is much larger than for the acid in crystalline form, as in tablets containing iopanoic acid. When the amorphous precipitate reaches the intestine, it is rapidly dissolved and therefore also quickly absorbed. In addition, the sodium salt of iopanoic acid is water soluble and as such it is more readily absorbed even in patients with achlorhydria, *i. e.* in whom the contrast medium does not react with hydrochloric acid in the stomach.

Toxicity. KNEIPP, who studied the toxicity of iopanoic acid and of its sodium salt, gave 22 g/kg bodyweight (confidence limits 34.1 to 14.2 g/kg) as the oral LD_{50} of the acid and 2.32 g/kg bodyweight (confidence limits 3.15 to 1.75 g/kg) for the sodium salt for mice, a difference of about one potency higher for the sodium salt. On comparison with the toxicity found by other research workers we see a wide variation in the oral toxicity of the acid. WINZER, LANGECKER, JUNKMANN (1954) gave the oral LD_{50} as 3.87 g/kg bodyweight for mice and HOPPE & ARCHER (1953) 15.8 g/kg.

The toxicity for sodium salt per os differs but slightly from KNEIPP's results. WINZER, LANGECKER, JUNKMANN gave the oral LD_{50} for sodium salt as 2.45 g/kg bodyweight. The difference in toxicity tests between the acid and sodium salt administered orally can only be explained in terms of quicker and more complete absorption of the sodium salt.

Cholecystography with the sodium salt of iopanoic acid. We have now used as a contrast medium the sodium salt of iopanoic acid (Bilijodon-Natrium, LEO) in 200 cholecystographies. As to the frequency with which filling of the gallbladder was obtained in this small material, the medium did not differ from iopanoic acid. As a rule, good filling was obtained with a dose of Bilijodon-Natrium 4 tablets (2.0 g), and 6 to 8 tablets (3.0 to 4.0 g) was regarded as being an adequate dose under all circumstances.

An advantage of Bilijodon-Natrium is the lower frequency of contrast remnants in the digestive tract. In that part of our series in which a dose of 4 tablets was used, contrast material was afterwards seen in 8.5 per cent of cases (6 cases out of 72). When 6 tablets were used, the frequency increased to 13 per cent (17 cases out of 128). The corresponding frequency for iopanoic acid was 43.5 per cent (Bilijodon 6 tablets: 20 cases out of 46). RENCK (1954) gave 53 per cent for Telepaque in a dose of 6 tablets. The remnants, when using the sodium salt, were furthermore much smaller than when using the acid.

The possibility of a much lower frequency of contrast remnants after cholecystography with Bilijodon-Natrium being due to chance, or to a more thorough preparation by enemata, could be excluded by the fol-

lowing observations. 1) Six patients who had received Bilijodon-Natrium were selected at random and examined without a previous enema. In none was any residual contrast medium observed. Roentgenography of these patients included not only ordinary films of the biliary region but also a conventional film of the abdomen. 2) The Bilijodon-Natrium group included 7 patients who had been examined previously with iopanoic acid (Telepaque). The interval between the 2 examinations varied between 3 days and 2 years. Residual contrast medium was demonstrated in films of the right hypochondrium, in all of these patients, after cholecystography with Telepaque, but in none after examination with Bilijodon-Natrium. Moreover, residual contrast medium has not been observed, as yet, after the administration of Bilijodon-Natrium in a patient in whom previous cholecystography with Telepaque had not also been followed by the formation of opacities in the intestine.

The above-mentioned figures and circumstances clearly show that from this point of view the sodium salt of iopanoic acid is preferable to preparations of iopanoic acid. It is true that the contrast remnants from iopanoic acid in the intestinal tract do not produce any serious difficulties as long as the gallbladder is functioning, but when no filling of the gallbladder is obtained, and a fair amount of contrast medium appears in the digestive tract, the question arises whether sufficient amount of the contrast medium has been absorbed. This disadvantage may be eliminated by using the sodium salt in place of the acid. A faint filling of the ductus choledochus is a further sign of sufficient absorption.

It was of interest to note that side-effects were roughly equal after both types of contrast medium. If the side-effects were due to the toxicity of the preparations, they would have been more frequent after the use of Bilijodon-Natrium because of the better absorption of this agent. Diarrhoea occurred in 7 per cent of the patients who received 4 tablets of Bilijodon-Natrium, and in 26 per cent of those who received 6 tablets. The corresponding figures given by WHITEHOUSE & MARTIN (1953) for Telepaque in a dose of 6 tablets were 25.3 per cent and by PÅLSSON for the same substance in a dose of 12 tablets, 29 per cent.

In the present series, Bilijodon-Natrium in a dose of 4 tablets was never followed by vomiting, and in a dose of 6 tablets occurred in 4.7 per cent of cases. RENCK (1954) reported vomiting in 3 per cent of cases following Telepaque in a dose of 6 tablets.

SUMMARY

Cholecystography with a new contrast medium Bilijodon-Natrium, the sodium salt of iopanoic acid, showed that the preparation is practically completely absorbed, with little or no residual contrast medium in the intestinal tract. The preparation produces at least the same degree of filling of the gallbladder as iopanoic acid.

ZUSAMMENFASSUNG

Die Cholecystographie mit einem neuen Kontrastmittel, Bilijodon-Natrium, dem Natriumsalz der Jopanoicsäure (N. N. R.) zeigt, dass es zu einer nahezu vollkommenen Absorption des Kontrastmittels kommt, wobei keine oder nur geringe Rückstände im Verdauungskanal verbleiben.. Es wird eine gleich gute Gallenblasenfüllung wie mit der Jopanoicsäure erhalten.

RÉSUMÉ

La cholécystographie au moyen d'un nouveau produit de contraste, Bilijodon-Natrium, sel de sodium de l'acide iopanoïque, a montré que ce produit est pratiquement complètement absorbé, ne laissant que peu ou pas de résidu de produit de contraste dans l'intestin. Ce produit donne au moins le même degré de remplissage de la vésicule biliaire que l'acide iopanoïque.

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CHOLEGRAPHIC DEMONSTRATION OF CYSTIC DUCT OBSTRUCTION

by

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Biligrafin represents a considerable advance upon earlier contrast media, and several papers have recently appeared, in which results obtained and problems arising in practice are discussed. In this communication, the demonstration of obstruction of the cystic duct will be dealt with. In 102 of our cases, no filling of the gallbladder was obtained with the per os method (Bilospect which is 4-oxy-3.5-dijodphenyl-α-phenylpropionic acid) and no stones were visible; out of these, the gallbladder was filled in 60 cases after the administration of Biligrafin. In 32, cystic duct obturation was revealed, and in 10 cases only was the examination unsuccessful because of failure of excretion.

When the gallbladder was visualized by cholecystography the diagnosis of cystic duct obturation could be excluded; furthermore, the presence or absence of gallstones could be determined. If, on the other hand, the impermeability of the cystic duct was assumed from 'non-filling of the gallbladder', the examination was less decisive. Before Biligrafin was introduced, an operation was frequently performed if typical clinical symptoms were associated with the failure of gallbladder filling. Negative findings in oral cholecystography may, however, be due to various conditions. In 1954, SHAPIRO mentioned the following factors accounting for negative oral cholecystography: 1) Deficient ingestion of the contrast medium, when the patient failed to follow the instructions. 2) Delayed emptying of the stomach; 3) Disturbance in intestinal absorption; 4) Disorders of liver function; 5) Rapid evacuation of the gallbladder; 6) Physiologic biliary stasis; 7) Drug effect; 8) Absence of gallbladder due to earlier operation; 9) Obturating stone in cystic duct; 10) Marked alteration in the gallbladder mucosa; 11) Lactation.

Submitted for publication 6 March 1956.

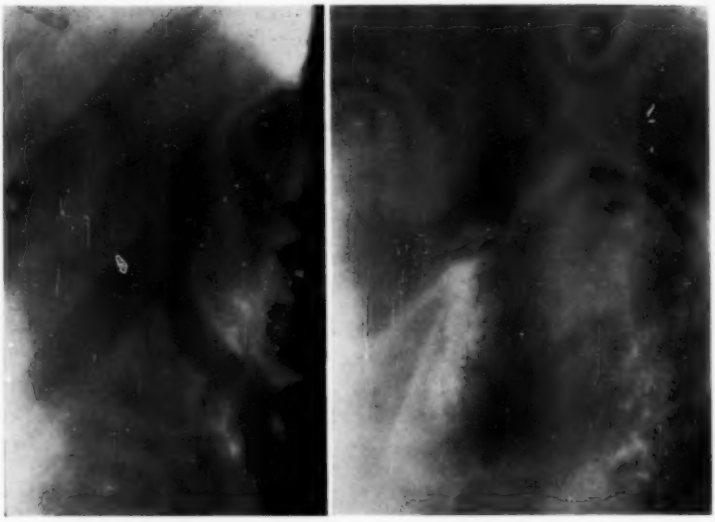

Fig. 1 Fig. 2

Fig. 1. Direct sign of cystic duct obturation 65 min. after injection of contrast medium. (After 200 min., no filling of gallbladder.)

Fig. 2. Direct sign of cystic duct obturation at neck of gallbladder 45 min. after administration of contrast medium. Cap-like impression at end of cystic duct. (After 240 min., no filling of gallbladder.) Operation: Gallbladder filled with stones.

Non-filling of the gallbladder in cholecystography is a frequent occurrence. WICKBOM and RENTZHOG observed it in 45 % of 1,340 cases and OLSSON in 50 % of his cases. Thus, the earlier methods did not offer direct or perfect proofs of cystic duct obturation.

The administration of Biligrafin has brought about a considerable change in this field (LANGECKER, HARWART and JUNKMANN, FROMMHOLD, HORNYKIEWYTSCH and STENDER). Due to its intense hepatotrophic and choleretic action, it gives a quick and reliable orientation about the extent of excretion, the pathway of the excreted bile, and about rate o outflow and storage of bile in the gallbladder. In cases with normal excretion of bile, the method of cholegraphy permits cystic duct obturation to be demonstrated directly. If the common bile duct is filled with contrast medium and the bladder is not outlined, the indications are that bile cannot pass into the bladder.

Cystic duct obturation is manifested in cholegraphy by direct or indirect signs. If the contrast medium, under the increasing pressure in the common bile duct, has passed into the cystic duct up to the site of

Fig. 3

Fig. 4

Fig. 5

Fig. 3. Indirect sign of cystic duct obturation 25 min. after injection of contrast medium. Good filling of common bile duct; no visualization of cystic duct. (After 300 min., no filling of gallbladder.) Operation: Distended gallbladder full of stones.

Fig. 4. The same patient. Late direct sign of cystic duct obturation 240 min. after injection. Common bile duct hardly visible; intense opacity in cystic duct obturated at the gallbladder neck; no filling of gallbladder.

Fig. 5. 70 min. after injection of contrast medium; dilated common bile duct, short obturated cystic duct. (After 240 min., no filling of gallbladder.) Operation: Gallbladder full of stones, its wall phlegmonous, dilated cystic duct; bean-sized stone at papilla Vateri.

obstruction, this may be taken as a direct sign. The head of the column may in this region terminate in a blunt and smooth outline (Fig. 1) or, having partly surrounded the obstacle, it may present a cap-like appearance. The length of the filled section of the cystic duct will vary, depending on the site of the obturation. A similar obstruction may be produced by a stone in the neck of the bladder or by many stones filling the lumen. In the latter case, the cystic duct will be filled in its whole length (Fig. 2). Cystic duct obturation appears as a direct sign less frequently. Out of our 414 cholegraphies, cystic duct obturation was present in 72 cases but as a direct sign in 17 only. In the majority of cases, the sign was indirect: the common bile duct was filled with contrast medium, but none had passed into the cystic duct (Fig. 3). The cause of this phenomenon is still not clear. GAEBEL and TESCHENDORF believe that the substance cannot pass into the cystic duct to the site of obstruction on account of the inspissated bile or mucus accumulated between the com-

mon bile duct and the site of obturation. Surgeons (MOLNÁR) have observed that the section under consideration may also be cicatrized. In patients later submitted to operation both conditions have been reported.

In 3 cases, cystic duct obturation was observed as a late direct sign. In the cholangiographic phase the indirect sign was revealed, and later, in the film taken 200 to 240 minutes after the administration of Biligrafin, the cystic duct was filled as far as the site of obstruction, as if the gallbladder had filled after the common bile duct had emptied (Fig. 4).

Cystic duct obturation may be due to various factors. From a practical point of view, the main cause is usually stones or inflammation, in most cases both in combination. Other conditions, such as tumours occur rarely. Cholegraphy may demonstrate cystic duct obturation but it gives usually no information as to the cause or its extent, which data are of less importance, however. In the unusual cases characterized by the simultaneous occurrence of cystic duct obturation and an external fistula of the gallbladder, intravenous cholegraphy and retrograde cholecystography (through the fistula) performed simultaneously may demonstrate the full extent of the obturation (LŐRINC and MÁRKUS). We have reviewed our material also from the viewpoint as to whether there were roentgenologic signs indicating for how long the cystic duct obturation had been present. Surgical experience has shown that cholecystectomy is followed as a rule by dilatation of the common bile duct. Since the general employment of cholegraphy, similar observations have been published. Generally, this dilatation is proportional to the time which has elapsed since cholecystectomy was performed, *e. g.* common bile ducts measuring 20 or 30 mm in width are not infrequent after cholecystectomies performed 10 to 20 years previously. This dilatation is mostly interpreted as a compensatory function of the common bile duct, which acts as a bile reservoir, whilst some authors (SAMUEL, LICHTMAN, MOLNÁR et al.) believe it to result from dyskinesia that was present before the operation. However, as cystic duct obturation from a functional point of view is a condition resembling that following cholecystectomy, the degree of dilatation of the common bile duct may in our opinion permit some conclusions to be made regarding the time at which cystic duct obturation had occurred. The symptoms of 48 of our patients dated back several years and there was justification for assuming that cystic duct obturation had persisted for a longer time. The width of the common bile duct was normal (from 2 to 8 mm) in 30 cases and increased (from 10 to 30 mm) in 18 cases. In contradistinction to this, in 22 of 24 patients with a short history, — symptoms having been present for less than six months — the width of the common bile duct was normal, and increased in only 2 cases.

Fig. 6

Fig. 7

Fig. 6. Error on account of an internal biliary fistula. 22 min. after injection of contrast medium: indirect sign of cystic duct obturation. (After 240 min., no filling of gallbladder.) Roentgen diagnosis: Obstruction of cystic duct.

Fig. 7. The same patient (G.-J. series) 3 days later. The barium passed from duodenum through a fistula into a shrunken gallbladder.

Dilatation of the common bile duct in cystic duct obturation may also be a manifestation of dyskinesia or a sequel of stone obturation which has ceased spontaneously. In our patients, the dilatation of the common bile duct was generally proportional to the time which elapsed since the onset of bile symptoms. This contention is fully supported by our cases with a short history; to a lesser degree by those with a longer one. Thus, within certain limits this observation offers the possibility of estimating the duration of cystic duct obturation.

In normal cases, the common bile duct is best visible at 40 to 80 min. after the injection of Biligrafin. Thereafter, the density of the contrast material in the ducts rapidly decreases but the filling of the gallbladder prevails. In the opinion of HORNYKIEWYTSCH and STENDER, bile duct filling lasting over two hours is pathologic; in more than half of our patients with cystic duct obturation, the common bile duct was still visible after two hours. In our view, the fact that the contrast material prevails in the ducts is due to the lacking reservoir function of the gallbladder. This is conceivable since the same quantity of contrast medium, in a case of cystic duct obturation has to be accomodated in regions of lesser

volume, until its outflow toward the duodenum begins. This sign, therefore, need not be regarded as pathological.

The demonstration of cystic duct obturation generally takes 2 to 4 hours. If the modification of ALDRIDGE is applied, this time may be shortened by about half that time, and by using LANGE's cholegraphic method to about 40 or 60 minutes.

Cystic duct obturation may be associated with stones in the common bile duct. Seven of our 42 cases operated upon had stone in this duct. In 5 of them, the stone in the common bile duct was visualized in the cholegraphy, in 2 it was not.

It must be emphasized that an internal fistula of the gallbladder may give rise to the erroneous diagnosis of cystic duct obturation because the contrast medium escapes from the gallbladder. This is another reason why the roentgenologic examination of the alimentary canal is never superfluous in cases of biliary symptoms and should also be carried out after the demonstration of stones in the gallbladder or bile duct. Such a case is illustrated in Figs. 6—7.

Cystic duct obturation sometimes occurs in a cystic duct remnant or in a gallbladder which has reformed after cholecystectomy (McDONOUGH and WISE, GLENN and JOHNSON). This condition cannot be demonstrated by cholegraphy, since, owing to the obstruction, the presence of the cystic duct remnant or reformed gallbladder cannot be confirmed either. Another difficulty in the differential diagnosis may arise from the extremely rare condition of congenital aplasia of the gallbladder (SCHINZ).

Conclusions

Cystic duct obturation may be recognized by means of cholegraphy with a security never attained by earlier methods. This condition is more often present than a stone in the common bile duct.

Cystic duct obturation may manifest itself by direct and indirect roentgen signs. The sign is termed direct if the opaque medium passes as far as the site of obstruction; it is comparatively rare. Both signs are reliable.

Longstanding cystic duct obturation is occasionally attended by dilatation of the common bile duct. In early cases this phenomenon is infrequent. The calibre of the common bile duct therefore admits of certain conclusions as to the duration of the obstruction. Cystic duct obturation is frequently associated with delayed passage of the opaque medium. This phenomenon is interpreted as being caused by the reduced volume of the space occupied by the outflowing bile.

SUMMARY

The demonstration by cholegraphy of obstruction of the cystic duct is discussed in detail. Direct and indirect signs of the condition are distinguished.

ZUSAMMENFASSUNG

Der Nachweis eines Verschlusses des Ductus cysticus mit Hilfe der Cholegraphie wird eingehend besprochen. Direkte und indirekte Symptome dieses Zustandes werden beschrieben.

RÉSUMÉ

Les auteurs étudient en détail la mise en évidence de l'obstruction du canal cystique par cholégraphie. Ils distinguent les signes directs et indirects de cette affection.

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THREE CASES OF EOSINOPHILIC GRANULOMA OF THE PELVIS IN CHILDREN

by

Lorentz Nitter

In 1940, OTANI and EHRLICH, and LICHTENSTEIN and JAFFE, described a condition found particularly in children and young adults and characterized by the occurrence of solitary or multiple granulomas in the skeletal system. The histologic picture is characterized by large cells of the histiocyte type and eosinophile granulocytes. In rare cases the phagocytes may contain drops of neutral fat causing the formation of so-called scum cells. The condition is benign and is usually cured by radiotherapy in moderate doses. Surgical therapy with removal of the affected tissue may also be applied. In some cases, regression has been observed without any treatment at all.

OTANI and EHRLICH believed the condition to be a benign granuloma of the bone simulating a primary neoplasm. They called it a 'solitary granuloma of bone', as in all of their seven cases only one lesion was observed. The term 'eosinophilic granuloma of bone' was used by LICHTENSTEIN and JAFFE to denote a particular granulomatous lesion of bone which did not fit any existing classification. This name, which refers to a characteristic feature of the microscopic picture, has been one of the most commonly used ever since.

Similar conditions have been described earlier under other names, but the authors seem to have been unaware of the fact that they belonged to a pathologic entity. FINZI published a case in 1929 and described the lesion as a myeloma with a prevalence of eosinophilic cells. SCHAIRER considered the lesion to be an osteomyelitis with eosinophilic reaction and described two cases in 1938. While LICHTENSTEIN and JAFFE believed that eosinophilic granuloma is a disease *sui generis*, most authors

Submitted for publication 1 June 1956.

now consider that the condition is related to Letterer-Siwe's disease and Hand-Schüller-Christian's disease; it is generally felt that these conditions are different stages of the same basic disorder of the reticuloendothelial system. Several cases have been published demonstrating transition from eosinophilic granuloma to Hand-Schüller-Christian's disease.

In Sweden, AHLSTRÖM and WELIN (1943) indicated the possibility that the condition represents a phase in the development of Hand-Schüller-Christian's disease or that it is a benign form of this condition. In Denmark, ENGELBRETH-HOLM, TEILUM and CHRISTENSEN (1944) described five cases in children between the ages of two and nine years, in which they observed a gradual transition to fully developed Hand-Schüller-Christian's disease. Finally, NIELSEN in 1945 described a case of an 8-year-old girl with characteristic lesions in the pubic bone and the right shoulder. The changes disappeared after a very low roentgen dose of 500 r. In Norway, HÖYER (1947) described a case of a 17-year-old boy, with the condition in the upper part of the right femur. Four months after surgical scraping the patient developed a spontaneous fracture through the previous granuloma cavity. The fracture healed after traction. No roentgen therapy was administered and no recurrences at the site or elsewhere occurred.

DUNDON et coll. in 1946 reviewed the literature to date and presented five new cases. They stated that up to that time a total of 53 cases had been described, including their own. Since then, several publications have appeared, especially from the United States. WILSON et coll. (1953) put the figure at 200 cases.

The etiology of the disease is still unknown. It occurs much more frequently in females than in males. For age distribution, reference may be made to DUNDON's paper, in which 64 % of the patients were under 20, and 37 % under 10 years of age, the oldest being 58. HAMILTON et coll. (1946) described nine cases, aged 19 to 32 years, from the American Army General Hospital. In 1953, GARSCHE discussed a congenital case in an infant girl with extensive osseous alterations in the right leg, which were verified microscopically. DUNDON found that of 53 published cases, 36 had solitary and 10 multiple localizations. In the remaining 7, the site was not given. In the 36 cases with solitary localization, the lesion was demonstrated only twice in the pelvis, in 13 cases in the cranium. SWAIN and WILLIAMS in 1953 reported a case with extensive cranial involvement which was first mistakenly diagnosed as meningioma.

As regards the site of predilection of the lesion in the skeleton, Fig. 1 is taken from KOTHE's paper (1953) which also contains an extensive bibliography. The most frequent situation is in the cranium, spine, pelvis, and ribs, followed by the long bones, with equal distribution in the

epiphysis, diaphysis, and metaphysis. In 1947, LOEHR described a case in a 22-year-old man with lesions in small long bones — in three fingers of the right hand. As far as is known, this is the only case which has been verified in the skeleton of the hand.

Roentgen examination usually reveals a round, or oval, sharply delimited osteolytic process. There is usually no surrounding osteoporosis and never a sclerotic border zone. There is usually no sequestration. WILSON et coll. demonstrated sequestration roentgenologically in one case and claim that even when a sequestrum is demonstrated the possibility of eosinophilic granuloma must be considered.

As regards symptoms, these may often be slight. In a number of cases the condition was discovered by chance, post mortem. In addition to vague indefinite pains in the affected region, there may in some cases be increased temperature, loss of weight, and, where there are multiple lesions, a poor general condition. The blood picture is usually normal but a slight eosinophilia and moderate leukocytosis may occasionally be present. The sedimentation rate may be normal or moderately increased. Phosphorus-calcium, phosphatase, cholesterin, and protein values in the blood are generally normal and the urine unaffected (ALTHOF 1953).

Fig. 1. Predilection of site of eosinophilic granuloma in skeleton (after KOTHE).

Case material

Since 1951, we have had three patients at the Norwegian Radium Hospital (N. R. H.), between the ages of one and two years, with this condition. In all three, the lesion was situated primarily in the pelvis, and in two of them it remained solitary. As the roentgen appearances in all of them were typical, and the treatment by reason of the situation difficult, they deserve a detailed description.

Case 1. 1996/51. Å. C. A. female, aged 2 ½ years. Six weeks before admission, in October 1951, the child began to complain of pain in the abdomen and left leg and limped. A roentgen examination of the pelvis was performed which showed cystic rarefaction in the left os ileum. Blood sedimentation 85 mm. Penicillin therapy was administered to deal with a possible osteomyelitis but the patient was transferred to N. R. H. as a tumour was suspected. On admission the patient had no pain and no clinical signs. Afebrile. Blood sedimentation 26 mm. Blood otherwise normal, no leukocytosis and

a b c

Fig. 2. Case 1. a) Eosinophilic granuloma of left ilium. b) 4 months later, after roentgen treatment. c) 3 years after (b): only traces of the lesion.

especially no eosinophilia. Roentgen examination of pelvis 24. 10. 51 (Fig. 2 a): Large area of destruction in the left ilium. Biopsy: Eosinophilic granuloma.

Roentgen therapy was instituted to left ilium. The field was chosen anteriorly as far laterally as possible and with a tangential radiation direction to avoid the ovary. Total dose 1,800 r (200 kV, 15 mA, filter 1 Cu, focal—skin distance 50 cm). A roentgen examination of the pelvis, 4 months later (Fig. 2 b), showed incipient filling, with some sclerosis of the granuloma cavity. No symptoms or clinical signs present. After a further 11 weeks, there was practically complete sclerosis of the granuloma cavity, and 3 years later (Fig. 2 c) only slight traces of the lesion were found.

The child has been examined regularly since then and has been perfectly well. A recent roentgen examination of the skeleton revealed no other lesions and no demonstrable disturbance of growth of the lower extremities.

Case 2. 25/53 O. N. male, aged 18 months, who a month previously had pain and limped with the left leg. A roentgen examination of the pelvis (Fig. 3 a) revealed a small osteolytic process in the left iliac bone which rapidly progressed. The appearances of the lesion, 17 days after the first examination, are shown in Fig. 3 b. On admission in January 1953 the child was afebrile and looked healthy. He was sensitive to palpation around the left ilium and limped when he tried to walk. Blood sedimentation 25 mm. Blood: Slight leukocytosis (W. B. C. 9,600) and 5 % eosinophilia. Through an incision over the iliac crest, soft, yellow-white almost myxomatous tumour masses, covered with a thin layer of bone, were exposed. Abundant tissue was removed for histologic examination but no radical scraping performed. There was considerable bleeding. Hist. exam.: Eosinophilic granuloma.

Roentgen therapy was administered on one field posteriorly toward the lateral aspect of the left ilium. Total dose 1,500 r (175 kV, 4 mA, filter 1 Cu, focal—skin distance

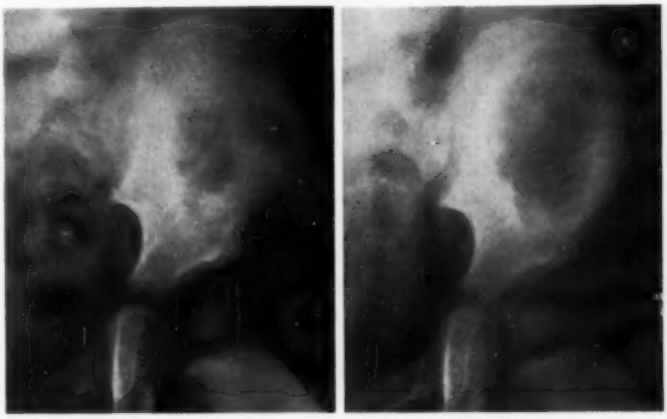

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Fig. 3. Case 2. a) Osteolytic lesion of left ilium. b) Marked progress 17 days later.

50 cm). As the process was practically unchanged at a control examination about 3 months after admission, an additional series of treatment was given with 1,200 r to the same field and under the same conditions. At the next roentgen control examination, 4 $^1/_2$ months later (Fig. 4 a), there were signs of incipient filling up of the granuloma cavity, and after a further 16 months, a general improvement. Three years after admission, only traces of the lesion were observed, Fig. 4 b. The patient had no clinical signs. There was no demonstrable inhibition of growth of the left leg, and complete roentgen examination of the skeleton showed no signs of further lesions.

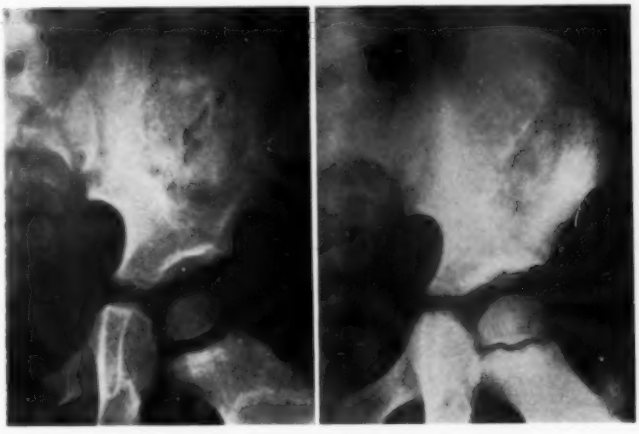

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Fig. 4. Same case as in fig. 3. a) About 6 months after roentgen treatment. b) After 3 years: only small changes still observable.

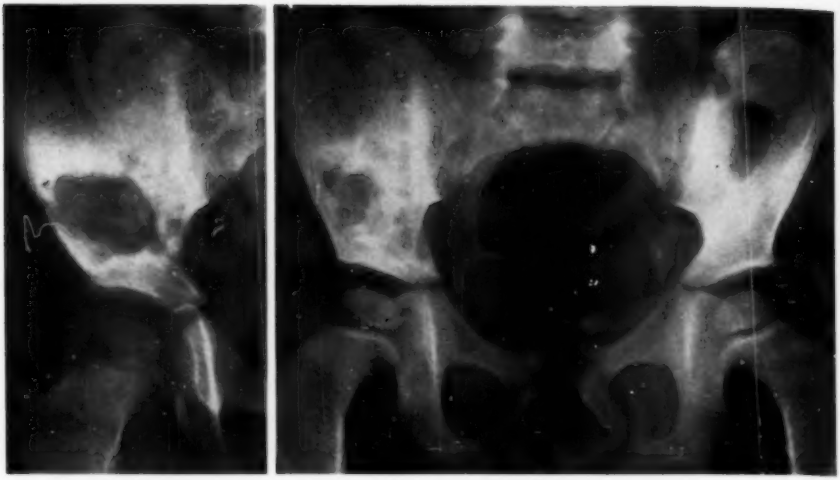

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Fig. 5. Case 3. a) Osteolytic lesion of right ilium. b) 3 months after operation: area of destruction filled by new bone; no change on left side.

Case 3. 1986/54. T. L. female aged 2 years. During the previous month her mother had noticed that the child's leg did not seem strong; she tired easily and would not walk. On admission in October 1954 there were no clinical signs. Roentgen examination of the pelvis (Fig. 5 a) showed a rather sharply defined large area of rarefaction in the lower part of the right ilium. Blood sedimentation rate 35 mm, Hgb 68 %, R. B. C. 5.3 m, W. B. C. 14,100. Blood cholesterol: 254 mg/100/ml. Serum proteins: total protein 6 %, albumin 4.9 %, globulin 1.1 %.

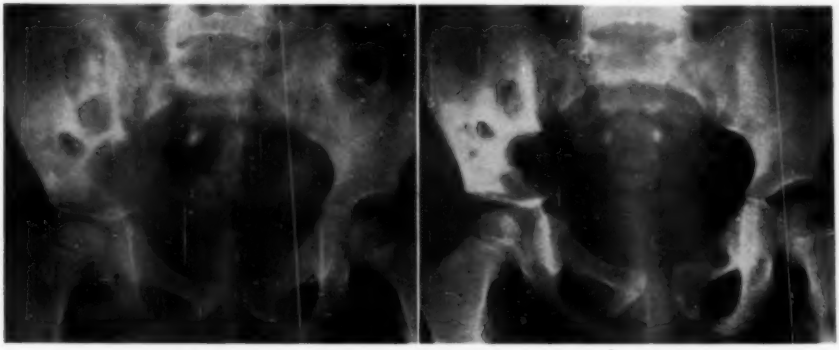

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Fig. 6. Same case as in fig. 5. a) 7 months after operation: progression of lesion and new destruction in left pubic bone. b) 9 months after operation: Sclerosis of the lesion treated with roentgen; progression on left side.

The diagnosis of eosinophilic granuloma was considered highly probable. As roentgen therapy was not desirable in this case, in order to avoid irradiation of the ovary, excochleation was performed in October 1954. Pathologic bone tissue was found in the region just above the acetabulum. A large cavity, filled with a soft grayish-yellow mass, was encountered below a thin cortical layer. All visible pathologic tissue was removed. Hist. exam.: Eosinophilic granuloma.

Fig. 7. Same case as in figs. 5 and 6; 13 months after admission: increased sclerosis on left side.

Roentgen examination of the pelvis 3 months later (Fig. 5 b) showed definite improvement with incipient filling of the granuloma cavity. Roentgen control after a further 4 months (Fig. 6 a) showed progression of the changes in the right ilium and irregular rarefaction in the left pubic bone.

As it was feared that the process in the right iliac bone might spread further, roentgen therapy was administered at this time with the beam directed as tangentially as possible to avoid the ovary. Total dose 1,000 r (170 kV, 10 mA, filter 0.5 Cu, focal—skin distance 30 cm). Roentgen control 2 months later (Fig. 6 b) showed progressive sclerosis of the granuloma cavity in the right iliac bone and increased destruction in the left pubic bone. Roentgen therapy was then administered to the left pubic bone with the beam directed downward. Total dose 600 r (170 kV, 10 mA, filter 0.5 Cu, focal—skin distance 40 cm). During the patient's stay in hospital, 2 small cavities were found in the left femur, and these were treated similarly. Further roentgen control (Fig. 7) showed continued sclerosis in the right iliac bone and incipient filling of the area of destruction in the left pubic bone. A complete examination of the skeleton in November 1955, 13 months after admission, revealed a small rarefaction proximally in the left tibia. Roentgen therapy was administered. Total dose 1,000 r (same factors as in the second treatment).

Ever since she was first admitted, the patient has been somewhat listless but looks well. The sedimentation rate remains high — 50 mm. W. B. C. 7,700, 8 % eosinophilia. Cholesterol in blood: 290 mg/100 ml. Serum proteins: total protein 7.8 %, albumin 3.47 %, globulin 4.33 %.

Discussion

As appears from the case reports, roentgen therapy was applied exclusively in our two first cases, after the histologic diagnosis had been made, in one case, by means of biopsy, in the other from affected tissue removed by scraping which involved only minor surgery. In the third case, only surgery in a form as to ensure what was believed to be radical removal of the affected tissue was performed at first. This case showed marked progression so that it was necessary to administer roentgen therapy six months later. In two of our cases (Cases 1 and 3) we had

the problem of a granuloma situated in the pelvis in young girls. It was for this reason that surgical treatment was applied in Case 3. In Case 1, there were several reasons for administering radiotherapy primarily. In adjusting the roentgen apparatus we attempted to avoid the ovary as far as possible by using a small field and directing the beam tangentially.

It is noteworthy that in our first two cases roentgen therapy gave very good results with rapid healing. No new localizations have been detected after four and three years control, respectively. The total roentgen doses administered were 1,800 r and 2,700 r, respectively, as Case 2 received additional treatment. No inhibition of longitudinal growth has been observed in these two patients.

It seems that the surgical treatment in our third patient has been a failure. Here, too, the lesion was a solitary one to begin with. But new localizations developed, and because of the extensive changes we could not take the chance of allowing the process in the pelvis to progress, in spite of the fact that our radiotherapy may possibly have involved some risk for the ovary. The roentgen dose here was reduced to 1,000 r and further control revealed rapid filling of the granuloma cavity. Only 600 r were administered to the granuloma in the left pubic bone, also with satisfactory results. It is reasonable to assume that it is generally possible to obtain good effects with a moderate roentgen dose. However, in Case 2 there was regression after a relatively high total dose.

In consideration of the primarily good results of roentgen therapy in the first two cases, it may be assumed that such a radical intervention as that performed in our third case may possibly have been a contributory factor to the dissemination of the disease to other parts of the skeleton. In any case, the defect in the right iliac bone after surgery is unnecessarily large.

The disease is probably more frequent than would appear and, as in other conditions, it is important to be aware of it. It is striking that two of our cases were referred to us from the same roentgen department in the course of a short time. In all three cases, the roentgen appearances are so typical that in conjunction with the slight clinical signs should afford the basis for a reasonably probable diagnosis. The rapid progression of the lesion in Case 2, in the course of only a little more than two weeks between the first and second roentgen examinations, is very striking.

As already mentioned, the lesion remained solitary in two of our cases; in the third several new localizations developed. Only further control can yield information as to whether this is simply a case of multiple lesions or whether further development will show transition to the next phase of the disease. The fact that the sedimentation rate is still high, together with the newly detected localizations, indicates that the disease is still in an active phase.

SUMMARY

After a brief review of the literature the author presents three cases, aged between one and two years, with primary solitary eosinophilic granuloma in the pelvis. The situation of the lesions presented some problems from a therapeutic point of view. In the two cases treated exclusively with roentgen the lesion remained solitary. In the third case, first treated by means of radical scraping, there was progression and development of several further lesions; subsequent roentgen therapy had a favourable effect. In all cases, the roentgenographic appearances were typical.

ZUSAMMENFASSUNG

Nach einer kurzen Besprechung der Literatur beschreibt der Verfasser 3 Fälle, zwischen 1 und 2 Jahre alt, von primären solitären eosinophilen Granulom im Becken. Die Lage des Granuloms ergab einige therapeutische Probleme. In 2 Fällen, die ausschliesslich mit Röntgenstrahlen behandelt wurden, verblieben einzelne Granulomreste. Im dritten Fall, bei dem es nach Radikaloperation zu einem Recidiv kam, hatte die folgende Röntgentherapie einen günstigen Erfolg. In allen Fällen waren die röntgenologischen Erscheinungen typisch.

RÉSUMÉ

Après une brève revue de la littérature, l'auteur présente trois cas, âgés d'un à deux ans, de granulome éosinophile primitif solitaire du bassin. Le siège de ces lésions a posé, du point de vue thérapeutique, certains problèmes. Dans les deux cas qui ont été traités exclusivement par roentgenthérapie, la lésion est restée solitaire. Dans le troisième cas, traité d'abord par curettage radical, il y eut progression et apparition de plusieurs autres lésions; la roentgenthérapie ultérieure eut un effet favorable. Dans tous les cas, les aspects radiologiques étaient typiques.

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CALIBRATION OF THE PORTABLE SWEDISH FREE-AIR CHAMBER EQUIPMENT AT THE U. S. NATIONAL BUREAU OF STANDARDS[1]

by

R. Thoraeus and *H. O. Wyckoff*

An investigation of the primary Swedish roentgen ray standard chamber equipment for the purpose of comparing it with some standards abroad was started (2,3) by THORAEUS in 1953. To facilitate this program a new portable chamber was constructed, of smaller dimensions than the primary standard chamber so that it could be transported easily. Its dimensions were such as to be nearly adequate for roentgen potentials of up to 175 kV. Results of the calibration of this chamber, carried out at three standardization laboratories, could then be compared with a comparison of the portable and primary Swedish chambers. The last of the three calibrations of the portable chamber was completed during a visit in February 1956 to the Radiation Physics Laboratory of the National Bureau of Standards in Washington. There, the portable free-air chamber equipment, designed and assembled by THORAEUS in 1952—1953, was calibrated with the NBS primary standard chamber (1,4) A brief account of the results of this calibration is given in the following.

The portable free-air chamber is cylindrical, with a length of 630 mm, and a diameter of 190 mm. On a single axis within the chamber and parallel to the axis of the chamber are three cylindrical electrodes consisting of a central collecting electrode, 200 mm in length and 20 mm in diameter, and two guard electrodes, each about 240 mm in length

[1] Presented by R. Thoraeus at the Seminar of the International Commission on Radiological Units and Measurements in Geneva, Switzerland, 5 April 1956. Submitted for publication 2 July 1956.

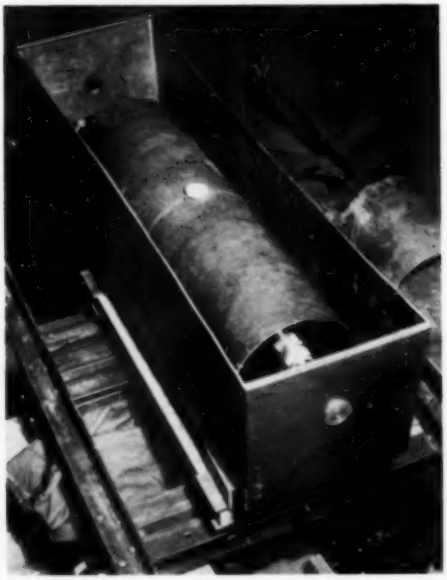

Fig. 1. The portable, cylindrical free-air chamber in the protective lead box with cover removed.

and 20 mm in diameter. The maximum distance between the electrode and the cylinder is 124 mm. The roentgen beam traverses the chamber parallel to the axis.

The potential between the electrode and the cylindrical shell was about 4,000 volts. By a separate investigation it was found that the potential could be reduced to 1,200 volts without changing the ionization current by more than 0.1 percent at the exposure dose rate used, about 3 r per min. In addition it was found that the ionization current was independent of the polarity of the collecting electrode. It was also found in a separate investigation that the insulators supporting the electrode do not disturb the electrical field in the chamber.

During the measurements, the free-air chamber was positioned in a lead box provided with a removable cover (fig. 1). The potential of this box could be changed from zero to about 4,000 volts with respect to ground without changing the ionization current. For convenience, the box is normally kept at ground potential. From these experiments it appeared that the box did not distort the collecting field and that 4,000 volts was adequate for saturation.

The roentgen protection of the chamber was also separately investigated. Each diaphragm was provided with a special lead plug which could be inserted in the diaphragm used, close behind the aperture, making possible the direct measurement of, and thus the correction for, any ionization current caused by leakage or stray radiation. No such ionization amounting to a correction of as much as 0.1 percent was observed during the calibration.

Both the NBS primary standard chamber and the Swedish chamber were positioned on a track perpendicular to the beam (figs. 2 and 3). The chambers could thus very easily be interchanged in the beam. Separate indicators made it possible to repeat the position of each cham-

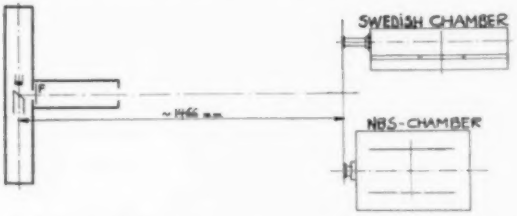

Fig. 2. Scheme of the experimental arrangement showing the respective chambers of the Institute of Radiophysics and of the National Bureau of Standards.

ber in the beam very accurately. The focal distance to the chamber diaphragms was checked by a cathetometer.

The collecting capacitor used with the Swedish chamber is constructed of coaxial brass tubes and has air as a dielectric medium, except at the ends where the tubes are mechanically fixed in position by small amber rings. The capacitor is protected against possible stray radiation by 3 mm lead + 1 mm brass. This capacitor was separately calibrated by the Resistance and Reactance Section, Electricity and Electronics Division of the National Bureau of Standards. The result was 204.2 ± 0.2 micromicrofarad. This value agrees within 0.05 percent with the corresponding values previously obtained in England in 1953 and in Western-Germany in 1954. This result shows that the capacitor has the very high constancy required for this purpose.

Fig. 3. View of the two chambers on the track (to the right), and the enclosed roentgen tube (to the left).

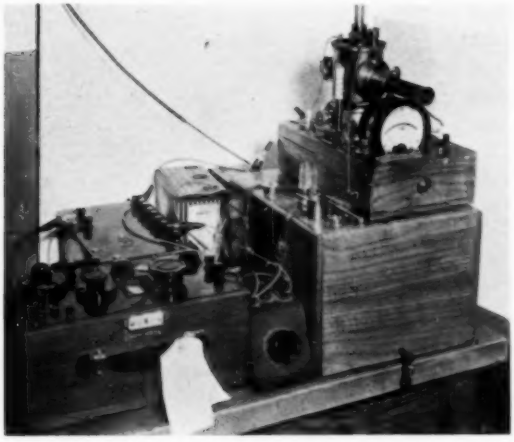

Fig. 4. The Swedish portable electrometer unit.

A Lutz-Edelmann single string electrometer with knife edges was used in a Townsend compensating circuit for measuring the ionization current in the portable chamber (fig. 4). The electrometer sensitivity was 14.7 scale divisions per volt, and compensation potentials of 30 to 50 volts were obtained.

The complete ionization current measuring equipments of both the free-air units were directly compared, one against the other. They agreed to within 0.1 percent.

The area of the Swedish beam limiting diaphragm (nominally 8 mm diameter) was determined from measurements of the ionization produced in the NBS ionization chamber, using first the NBS and then the Swedish aperture, and from the known area of the NBS aperture. Measurements of the diameter of the Swedish diaphragm indicated a slight coning. It was not possible to measure the diameter of the cone at the defining plane, so the area determined by ionization measurements was used in the calibration.

A second diaphragm is sometimes used to reduce the scatter from the defining aperture. In agreement with earlier results at NBS, and also at the National Physical Laboratory in England, such a diaphragm did not change the ionization collected in the Swedish chamber.

Corrections applied to the radiation measurements with the Swedish chamber before comparison with those of the NBS chamber included: 1) a correction for the ionization measurement of 0.1 percent; 2) a correction for the aperture area of 0.5 percent; 3) a correction for ionization from secondary photons and inadequate chamber size of from -0.3 percent at the lowest kilovoltage to $+0.9$ percent at the highest kilovoltage; 4) a correction for the differences in the air absorption, in the path between the diaphragm and the collecting volumes, of from 0.5 percent at the lowest kilovoltage to 0.2 percent at the highest kilovoltage. In the following table, the ratios of the corrected NBS results, B, to the corrected Swedish results, S, are given.

It is interesting to compare the results of the previous calibration of the Swedish chamber at Frankfurt (3) with the present results. The results previously reported are without any corrections applied to the Swedish chamber. From measurements made at NBS, the diaphragm used at Frankfurt did not require a correction. Air absorption corrections were not required, as the collecting volumes were at the same distance from the target. It is assumed that no correction is required for the Swedish ionization measuring equipment. The ratios of the Frankfurt results, F, to the Swedish results, S, obtained after applying corrections for the secondary photon contribution and inadequate chamber size, are also given in the table. Except for the one point at 100 kilovolts, the agreement seems to be very good and indicates that calibrations of the same chamber by Frankfurt and NBS are possible to a precision of about 0.5 percent. As these two standards are of very different construction and size, the correction factors now available ought to be reliable.

Table

Results of Swedish chamber calibration

Tube voltage kV	Added filter mm	H.V.L. mm Cu	Ratio B/S after all corrections	Ratio F/S after all corrections
52	0	0.05	—	1.001
60	0	0.085	1.005	—
70	0	0.10	—	1.002
75	0	0.11	1.008	—
100	1 Al	0.19	1.005	—
100	0.11 Cu + 1 Al	0.24	—	0.995
150	0.25 Cu + 1 Al	0.61	1.006	—
150	0.33 Cu + 1 Al	0.70	—	1.005
170	0.33 Cu + 1 Al	0.83	—	1.002
200	0.5 Cu + 1 Al	1.2	1.004	—
250	1 Cu + 1 Al	2.1	1.003	—

SUMMARY

The authors give a brief account of the results obtained in the calibration of the portable Swedish free-air chamber equipment with the free-air standard chamber equipment of the Radiation Physics Laboratory of the National Bureau of Standards, Washington. These results are compared with a similar calibration at Frankfurt.

ZUSAMMENFASSUNG

Die Verfasser geben einen kurzen Bericht über die Ergebnisse, die beim Vergleich des transportablen schwedischen Standard-Messgeräts mit dem festen Standard-Messgeräts des Strahlenphysikalischen Laboratoriums der National Bureau of Standards in Washington gewonnen wurden. Die Resultate werden mit denen in Frankfurt früher ausgeführten Untersuchungen verglichen.

RÉSUMÉ

Les auteurs rendent brièvement compte des résultats obtenus par l'étalonnage de l'équipement portatif suédois de chambre à air libre au moyen de l'équipement étalon de chambre à air libre du Laboratoire de Physique des Radiations du National Bureau of Standards, Washington. Ces résultats sont comparés à un étalonnage semblable fait à Francfort.

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FROM THE NATIONAL PHYSICAL LABORATORY (DIRECTOR: G. B. B. M. SUTHERLAND), TEDDINGTON, ENGLAND, AND THE NATIONAL BUREAU OF STANDARDS, WASHINGTON, D. C., U. S. A.

AN INTERCOMPARISON OF THE ROENTGEN STANDARDS OF GREAT BRITAIN AND U. S. A.

by

G. H. Aston and *F. H. Attix*

An intercomparison in 1953 of the National Physical Laboratory (NPL) primary roentgen standard ionization chamber with a recently constructed and much larger National Bureau of Standards (NBS) primary chamber confirmed that the NPL chamber was of inadequate dimensions for roentgen rays generated at voltages above about 80 kV. A new chamber, intended to be used with roentgen rays generated up to 300 kV, was therefore constructed at NPL during 1954. In March 1955, the new chamber was taken to Washington for an intercomparison with the NBS chamber. The present paper gives the results of this intercomparison.

Details of the chambers and experimental arrangements. An isometric sketch and some details of the NBS chamber have been published (Wyckoff, Aston and Smith 1954; Wyckoff and Aston 1954). The only significant changes which have been made since 1953 are that an additional set of guard-wires have been fitted, the distance from the chamber aperture to the collector electrode has been reduced and the scattering diaphragm has been removed, and there is a new capacity compensator with a vibrating reed electrometer as a null instrument. A section of the chamber is shown in Fig. 1. The collector plate height is 26.8 cm.

A brief account of the NPL chamber with photographs has been given by Smith (1955). Additional double guard-wire systems have been fitted at the front and rear of the electrode assembly. Most of the important dimensions are given in the section shown in Fig. 2. The height of the collector plate is 30 cm. The current compensator is of the conventional

Submitted for publication 29 June 1956.

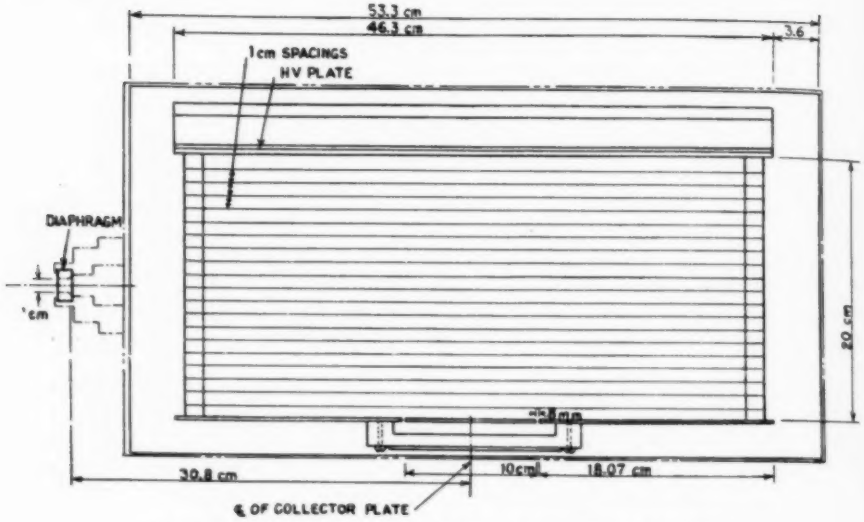

Fig. 1. Sectional view of NBS free-air ionization chamber.

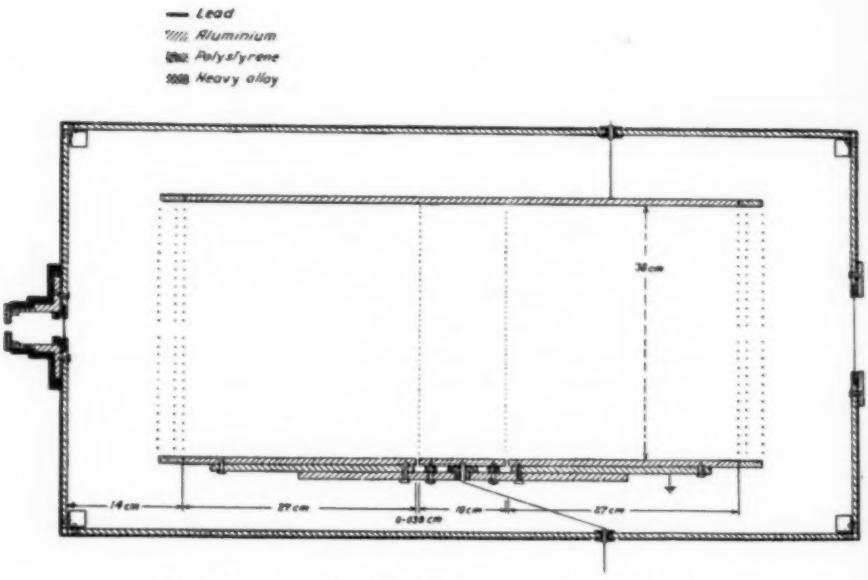

Fig. 2. Sectional view of NPL free-air ionization chamber.

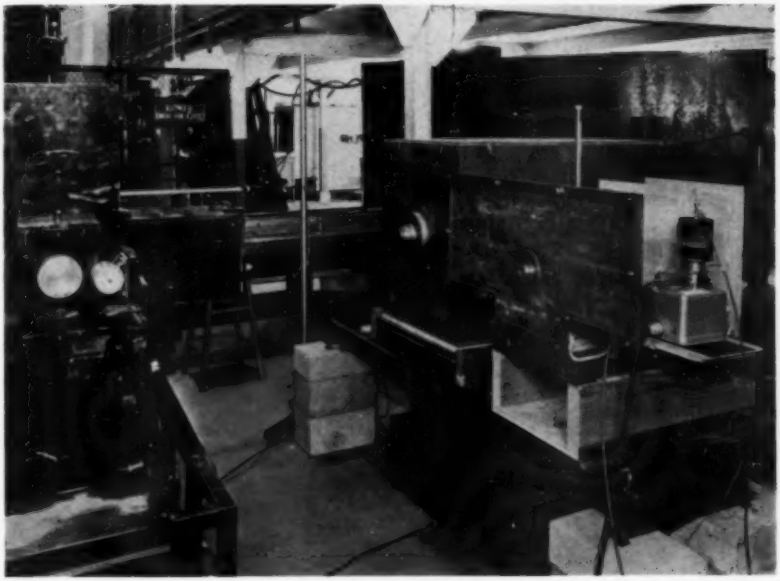

Fig. 3. NBS and NPL free-air chambers set up for intercomparison.

type with a Lindemann electrometer but has a specially designed capacitor.

A track was set up at NBS perpendicular to the roentgen beam, and the chambers were mounted on carriages moving on the track so that each could easily be brought in turn into the beam, as shown in Fig. 3. The chambers were initially aligned to the roentgen beam, and the alignment was checked periodically with a telescope. The effective limiting plane of the diaphragm was very nearly the same for each chamber, at a distance of about 102 cm from the roentgen tube focal spot, and the very small displacement between these planes was measured and allowed for on inverse square law, by recording the position for each chamber with a travelling telescope on each occasion when the chamber was moved into place for measurements.

The tube output was kept very nearly constant during the measurements, at a particular quality, by stabilizing to a high degree both the high voltage and the tube current.

Procedure in intercomparisons and necessary corrections. The chambers were compared using roentgen rays generated at six voltages within the range 60 to 250 kV; the filtration, in addition to the inherent filtration (3

mm Al), increasing from none at the lowest voltage to 1 mm Cu plus 1 mm Al at the highest. At each radiation quality, the rate of collection of ions was measured several times alternately for each chamber, thus making it possible to allow for the small gradual changes in radiation output, usually less than 0.2 %, which occurred during a series of measurements. At most radiation qualities, the range of values for the ratio of the ionization currents of the two chambers, obtained from a series of measurements, was less than 0.1 % and the largest range was 0.14 %.

There are several corrections required before the charge collected per unit ionized volume can be converted into a figure giving the dose in röntgens, and these corrections are not identical for the two chambers because of their different dimensions and operating conditions. For the purpose of comparing the chambers, the magnitude of a correction need not necessarily be known for each chamber, since only the difference in the corrections for the two chambers is involved. For example, complete saturation is not achieved in either chamber, the deficiency being of the order of a few parts in 1,000. Each chamber is normally operated with 3,000 volts between the plates, giving 150 volts per cm for the NBS chamber and 100 volts per cm for the NPL. These normal operating conditions were used in the intercomparisons, but an additional measurement was made at each quality with 100 volts per cm on the NBS chamber, *i. e.* the NPL voltage gradient, and the correction for the difference in departure from saturation for the two chambers thus determined.

The other corrections are for difference in air absorption in the two chambers (because of a difference of about 22 cm in the distances from the chamber diaphragm to the centre of the collecting electrode), for incomplete utilization of ionization due to inadequate dimensions, for collection of ions due to absorption of scattered photons, and for uncertainty in the collecting volume because of field distortion. The first of these corrections was computed from the values for air absorption per metre used by NBS and by NPL. The corrections for the second and third effects have been determined at NBS (Attix and DeLaVergne 1954) and these results were used at the time of the intercomparison to estimate the values for the NPL chamber. Recent measurements on the NPL chamber have confirmed these estimated values for the effect of scattered photons to 1 part in 1,000.

The errors due to field distortion have been determined for both chambers by making measurements with the case at its normal earth potential and then with the case at the potential of the high-voltage electrode. The change will give an indication of the field distortion produced by the nearness of the earthed case, and the rate of collection of charge for no distortion will be approximately the mean of the values

for the two conditions. For the NPL chamber, the change in the rate of collection of charge was 0.2 % when the potential of the case was altered in this way. Thus it appears that the error due to field distortion is about 0.1 %. The corresponding error for the NBS chamber is 0.0 %.

The charge-measurement systems used with the chambers were compared with one another and were shown to agree to 0.02 %. Measurements of pressure and of the temperature of the air in a chamber were made before and after each set of readings. It was necessary to make allowance for temperature differences in the air in the two chambers, which were sometimes as much as 1° C.

Results of intercomparisons. The results of the intercomparison are given in the table below in the form of the ratio of the dose rate in röntgens measured by the NPL chamber to that measured by the NBS chamber, when the corrections stated above have been applied. There are two values for this ratio, depending on whether the NBS or the NPL air absorption data are used.

Table

Radiation quality			Ratio dose-rate NPL chamber to dose-rate NBS chamber	
Kilovolts (constant potential)	Added filtration (mm)	H.V.L. (mm copper)	NBS air absorption	NPL air absorption
60	None	0.077	1.005	1.006
75	None	0.099	1.005	1.006
110	0.097 Cu + 1.02 Al	0.34	1.004	1.004
150	0.228 Cu + 1.02 Al	0.60	1.003	1.003
200	0.52 Cu + 1.02 Al	1.23	1.003	1.002
250	1.02 Cu + 1.02 Al	2.14	1.005	1.004

Discussion of results and conclusions. The mean value over the whole quality range of the ratio of the dose rates measured by the two chambers is 1.004, whichever air absorption corrections are used. These differences of a few parts in 1,000 between the two chambers are not yet accounted for. Using the NPL air absorption data there is a slight tendency for the difference to decrease as the roentgen ray generating voltage is increased, but using the NBS air absorption data there is no systematic change with quality. The NBS air absorption data have been obtained recently. Those used at NPL were obtained a considerable time ago and it is intended to make a re-determination. It seems certain, however, that errors in air absorption data cannot account for most of the differences between the chambers.

Other sources of error have been examined. The possibility that the differing designs of the diaphragms might give rise to small discrepancies was tested by making measurements using each diaphragm alternately on one of the chambers. The results were consistent with the metro-

logically determined areas of the effective apertures to within 1 part in 1,000.

The intercomparison has shown that the chambers are consistent with one another to within a few parts in 1,000. This does not necessarily indicate that a dose can be determined absolutely in röntgens to quite the same accuracy, since in the intercomparison only the differences in corrections for the chambers are involved, and any errors in the corrections will be less significant than when corrections are being applied to the readings of a single chamber. It may be possible, therefore, to obtain an international consistency in measurements in röntgens, which is rather better than the absolute accuracy attainable without further extensive investigations.

Acknowledgment

The authors desire to thank Dr. H. O. Wyckoff, National Bureau of Standards, for valuable discussion of the results obtained in the intercomparison. The work described above has been carried out as part of the research programs of the National Physical Laboratory and the National Bureau of Standards, and this paper is published by permission of the Director of the Laboratory and the Director of the Bureau.

SUMMARY

The medium kilovoltage roentgen standard free-air chambers of Great Britain and the United States have been intercompared in the region 60 to 250 kV. A difference of approximately 0.4 % was observed in the exposure-dose as measured by the two chambers, nearly independent of the radiation quality.

ZUSAMMENFASSUNG

Die englischen und amerikanischen Standard-Messgeräte für den mittleren Kilovoltbereich der Röntgenstrahlung sind zwischen 60 bis 250 kV miteinander verglichen worden. Eine Differenz der Exponierungsdosis von etwa 0,4 % wurde bei Messungen mit den beiden Kammern beobachtet; der Unterschied ist von der Qualität der Röntgenstrahlung nahezu unabhängig.

RESUMÉ

Les chambres étalons de Grande-Bretagne et des Etats-Unis à air libre pour les rayons roentgen de moyen kilovoltage ont été comparées entre elles dans la région de 60 à 250 kV. On a observé une différence d'environ 0.4 % dans la dose d'exposition mesurée par les deux chambres, à peu près indépendante de la qualité des rayons roentgen.

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CYTOLOGIC STUDIES OF NIPPLE DISCHARGE

by

Olle Kjellgren

During the non-functional period of the mammary gland, there is normally no noticeable secretion. The ducts then constitute the main part of the gland system. The alveoli are small and covered with a thin epithelium with cuboidal or slightly columnar cells and the large ducts with one single layer of cuboid cells which becomes pseudo-stratified close to the nipple.

Secretion from the mammary gland other than in immediate connection with lactation is generally a sign of disease. The character of the discharge may range from watery uncoloured to yellow-green, light-brown, dark-brown, or bloody. Purulent discharge also may occur.

The reason for spontaneous discharge from the mammary gland — without any connection with lactation — may be an inflammatory condition, chronic glandular cystic hyperplasia, cystic fibroadenomatosis, intracanalicular papillomas, or a carcinoma growing intracanalicularly. When the discharge is bloody the cause more often is due to a neoplastic genesis than when the discharge is serous.

The bloody discharge has been given much attention in the literature owing to its connection with mammary cancer. NOHRMAN (1949) in his 1,042 cases of mammary cancer found that bleeding from the nipple occurred in 5 per cent. GESCHICKTER (1945) stated that 4 per cent, WOLPERS (1933) 1 per cent, and BLOODGOOD (1922) 1 per cent of such cases present this sign.

When reporting cases of bleeding from the nipple, different authors have indicated slightly varying frequences of mammary cancer. ADAIR (1930) in a material of 108 cases of bleeding from the nipple found 47 per cent had cancer, CAMPBELL (1946) 38 per cent among 55 patients, and GESCHICKTER (1945) 36 per cent in his 287 cases. GRAY and WOOD (1941) reported 50 per cent among 175 cases, and NOHRMAN (1949) 39 per cent in 109 cases. KILGORE, FLEMING and RAMOS (1953) found that of 103 patients with

Submitted for publication 7 May 1956.

bloody discharge from the nipple, every sixth patient had cancer or a condition in which the presence of cancer could not definitely be excluded. HINCHEY (1941) stated that cancer was the cause of nipple discharge in 36 per cent of 67 cases.

If the bloody discharge from the nipple is not connected with a palpable tumour in the breast, GESCHICKTER (1945) stated the frequency of cancer to be 9 per cent. NOHRMAN (1949) gave the frequency of cancer as 88 per cent if a tumour can be palpated at the same time.

The usual cause of bloody discharge from the nipple is intraductally growing papillomas. GESCHICKTER (1945) reported papillomas as the cause in 34 per cent of 287 cases of bleeding from the nipple and KILGORE, FLEMING and RAMOS (1953) 44 per cent of 103 cases. HAAGENSEN, STOUT and PHILLIPS (1951) found, when analysing 108 cases of intraductal papillomas, that 51 per cent had produced bleeding from the nipple and that 21 per cent had serous discharge. HINCHEY (1941) stated that about 11 per cent of cases with nipple discharge had papillomas and KILGORE, FLEMING and RAMOS (1953) that 8 per cent of 55 cases with serous discharge from the nipple showed papillomatous changes.

Various authors give chronic cystic mastitis as an etiologic cause of bleeding from the nipple with a varying percentage. The 7 per cent af ADAIR (1930) and the 4 per cent of GESCHICKTER (1945) are representative figures.

As a discharge from the nipple, especially when it is bloody, is very often a sign of potentially malignant or actually malignant disease of the breast, various methods of examination have been tried in order to arrive at a more accurate diagnosis. This is especially the case when the findings on palpation are normal and no discharge appears at the nipple when any particular part of the gland parenchyma is pressed. In cases in which the pathologic process can be localized by palpation, the most important method of examination is to excise a portion of the tumour. Aspiration biopsy has also been carried out (FIEBELKORN 1954). In cases in which palpation is normal, transillumination (CUTLER 1929) and roentgen examination of the soft parts (WARREN 1930) have been performed for diagnostic purposes. An important contribution was HICKEN's introduction of mammography in 1937, which facilitated the localization of the pathologic process; the method has been employed in Sweden (LOSELL 1940; FROSTBERG 1942; SANDBLOM and LÖFGREN 1952).

Cytologic studies of the nipple discharge. ADAIR (1930) mentioned that he had used stained smears of the discharge from the nipple, which on examination enabled the diagnosis of malignancy to be made or eliminated. He gave, however, no detailed description of the tumour cell findings.

The important work within exfoliative cytology by PAPANICOLAOU (1943, 1954 and 1955) has renewed the interest in the method of examining the nipple discharge microscopically for atypical epithelial or tumour cells. Several authors have described various cytologic appearances in the nipple discharge in connection with different patho-anatomic processes in the mammary gland.

The cytology of the mammary secretion is comparatively simple and is restricted to a few cells. Most cells are of a ductal origin and mainly arise from the large ducts. In most cases the discharge is very poor in cells, these mainly consisting of a few squamous cells from the ducts nearest the nipple and varying in size and shape. Furthermore, there are some cells which are generally small, appear singularly, and are often slightly wrinkled. The cytoplasm usually shows distinct vacuolation. In the larger cells the vacuolation is more predominant and gives the cytoplasm a foamy appearance; the nucleus is then often situated eccentrically and two or more nuclei may occur. The origin of these small and large cells is uncertain. The small cells probably originate from the epithelium in the ducts, but the larger, more vacuolized cells, very much resemble histiocytes. The fact that these cells occur to a very great extent in inflammatory conditions, including chronic mastitis, leads, according to PAPANICOLAOU, to the conclusion that they are really histiocytes.

The cell picture in chronic cystic mastopathy has been described by SAPHIR (1950) and PAPANICOLAOU (1954), inter alios. This condition involves an abundance of histiocytes and leukocytes in the secretion. The phagocytic elements have nuclear membranes, readily stainable. The nucleus is often vesicular and placed eccentrically. The cytoplasm is foamy, and vacuolized and the cells are sometimes signet-shaped. Individual squamous cells of typical appearance also occur, sometimes en bloc. Blood cells and blood pigment are also present.

When papillomas grow intraductally, epithelial cells occur shed off en masse, or in groups. The cells are often rounded or oval, the nucleus being remarkably large and sometimes occupying the greater portion of the cytoplasm; it is readily stainable and has distinct nuclear membranes. The appearance of the chromatin pattern is typically benign. A certain structural atypia and enlargement of the nuclei as well as hyperchromasia may occasionally occur and suggest malignant transformation.

With intraductally growing cancer there are tumour cells in the discharge in addition to blood and blood pigment as well as phagocytic cells. The size and appearance of the tumour cells vary. The cytoplasmic boundaries are generally indistinct and the nuclei large, hyperchromatic, and varying in shape and size among the cells. The chromatin is irregular and arranged in clumps; large nucleoli often occur. The tumour cells here and there reveal a phagocytic activity, so that the tumour cells engulf one another. A considerable vacuolation commonly takes place in the cytoplasm. The tumour cells occasionally appear alone, sometimes in small groups. The individual cells may be well preserved or cytolysis may have started. Naked cell nuclei may be present. Necrotic cells

sometimes occur in malignant conditions, but hardly in benign ones. Mitotic figures may also be seen, but very seldom occur.

During the period 1950—1952 SAPHIR reported his experience in 90 patients with PAPANICOLAOU's method for examining the nipple discharge. Of the 90 cases, 37 were cytologically negative and there was no case of chronic cystic mastopathy, papillomas, or cancer. There were 21 positive diagnoses of chronic cystic mastopathy; of these 21 cases, 1 was of papilloma and 2 of carcinoma, the other diagnoses being correct. Among 13 cytologic diagnoses, positive for cancer, there were 1 papilloma and 1 chronic cystic mastopathy; the other diagnoses were correct. Of seven diagnoses, positive for papillomas, there were 1 chronic cystic mastopathy and 1 cancer in situ; the others were correct. Of 5 diagnoses given as suggestive of cancer there were 4 carcinomas and 1 papilloma, and, finally, of 6 diagnoses of possible papillomas there were 3 papillomas and 3 cases of chronic cystic mastopathy. There were thus 2 cases of false positives. Among false negatives 1 papilloma, and 2 chronic cystic mastopathies were found. Of 11 uncertain diagnoses there were 4 carcinomas, 3 cystic mastopathies, and 4 papillomas.

In 1950 JACOBSEN reported a case of mammary cancer which had been diagnosed by examining the mammary discharge cytologically. In 1951 EISEN and TAFT described a case of Paget's disease, diagnosed by cytologic examination of the nipple discharge. In 1955 SICARD, FLABEAU, and MARSAN accounted for 11 cases of discharge from the nipple, examined by PAPANICOLAOU's method. Two of the cases were not operated on and were excluded from further analysis. Among the 9 remaining cases, 7 were cytologically negative. One of these had mastitis, 5 had benign intracanicular proliferations and 1 undifferentiated cancer. Consequently, 1 case of cancer was cytologically negative and 2 positive. Both these cases had malignant tumours on histologic examination.

JACKSON and SEVERANCE (1946) reported on a clinical material of 584 cases. A discharge could be pressed out from 974 mammae for examination; 843 of these had no tumour cells and 131 contained such cells. The authors did not use PAPANICOLAOU's technique but stained with Wright's solution. A condition for diagnosing tumour cells was that they readily absorbed the stain and that most of them were not vacuolized. The cells should also vary in size and shape and appear together in groups of two or more. Most of them which fulfilled these demands originated from duct papillomas or papillary cystadenomas. Of the 131 patients who had a discharge with tumour cells, 80 were not operated on. Of the remaining 50, papillomas or cancer could be found in 38 or 74.5 per cent. In 13, neither papillomas nor cancer could be found, corresponding to 25.5 per cent of the 51 patients operated on. In 36 patients, red blood cells occurred together with tumour cells; 10 of these were not operated on, but of the remaining 26 the diagnosis was papilloma in 18, carcinoma in 5, and neither of these conditions could be determined in 3. If there were red blood cells in secretion but no tumour cells it was possible, in 7 cases operated on, to prove 4 cases of papilloma and 3 of cancer.

JACKSON (1951) and JACKSON, TODD and GARSUCH (1951) have reported further experiences of the cytologic diagnosis of the nipple discharge, especially in papillomas of the milk ducts.

Own investigations

The method of examining the nipple discharge cytologically has been tried at the Department of Radiotherapy in Gothenburg, since April 1954. It has been used in 39 cases sent for consultation because of discharge from the nipple or in which this has been the most notable finding.

Of the 39 patients, 21 or 55 per cent had discharge which they had not considered bloody. On examination, however, 3 of the 21 had a macroscopically blood-stained discharge. The discharge had been described as bloody by 17 patients or 45 per cent, 3 of which, however, proved to have a macroscopically serous discharge. One patient was referred for a mass in the breast and a discharge which was not mixed with blood. This also tallied with the objective finding. One patient had only pain and tenderness in the breast and on examination was found to have an abscess. Four patients had pain and tenderness in the breast, and discharge which was in one case bloody and in three serous.

Of the 21 patients who complained of serous discharge, 18 had a macroscopically serous discharge, but in 12 the discharge was microscopically bloody, and 9 patients had only a slight admixture of blood. Of the 17 patients who came to the hospital because of a bloody discharge, 15 had a microscopically bloody discharge, while in 2 cases the discharge was microscopically serous (Table 1).

Table 1

Correlation of the symptoms with the signs

Symptoms	Signs				Total
	Serous discharge		Bloody discharge		
	Macro	Micro	Macro	Micro	
Serous discharge	18	9	3	12	21
Bloody "	3	2	14	15	17

The age distribution of the 39 patients is shown in Table 2.

Table 2

Age distribution	Number of cases
25—29	3
30—34	4
35—39	7
40—44	8
45—49	8
50—54	3
55—59	1
60—64	2
65—69	3
Mean age	44.2

The mean age of the cases is 44.2 years. If consideration is taken of the various objective findings it is found that patients with a serous secretion had a mean age of 43 years and those with a bloody secretion a mean age of 46 years. In 13 patients, or 1/3 of the case material, who

had a palpable resistance at the examination, the mean age was 48 years. Possibly there is an age trend in relation to the objective findings, but the various mean ages are not significantly different.

The entire material consisted of 39 patients, 24 of which were examined by mammography. Of these examinations, 7 were a technical failure or impossible to accomplish. A positive result was achieved in 11 mammographies, and 6 were negative. Operation was performed on 14 of the 24 patients examined by mammography, the histologic diagnosis compared with the findings on mammography is shown in Table 3. Positive mammography in 11 cases revealed 4 cases of papillomatosis; of the 6 negative cases, one had papillomatosis. Cancer was found in none of the mammographically examined patients.

Table 3

Histologic findings in patients mammographically examined and operated on

Mammographic findings	Number of cases	Histologic diagnosis				
		Oper.	Cancer	Papillomas	Atypical	Cystic fibroadenomatosis
Positive	11	10	0	4	[2] 1 (2)	[1] 4 (9)
Negative	6	2	0	1	[3] 1 (2)	[4] 0 (2)
Technical failure	7	2	0	0	0	2
Total	24	14	0	5	2 (4)	6 (13)

[1] 3 cases of papillomatosis also had cystic fibroadenomatosis.
2 had atypical signs.
[2] plus 1 patient with papillomatosis.
[3] " 1 " " "
[4] " 1 " " atypical signs.
" 1 " " papillomatosis and atypical signs.

Of the 39 patients in the case material, 13 had a palpable mass on examination; of these, 9 were operated on. The histologic diagnosis revealed cancer in 3, papillomas in 3, and galactocele in one. The only finding in 1 patient was cystic fibroadenomatosis. This diagnosis, however, occurred also in 3 of the above-mentioned patients with other diagnoses. One patient had a mammary abscess. There were 2 with atypical signs, both of which had cystic fibroadenomatosis.

The cytologic examination

Taking of samples. The nipple discharge taken for cytologic examination was treated according to PAPANICOLAOU's technique. A slide was pressed against the nipple if a discharge appeared spontaneously or could

Papanicolaou staining procedure

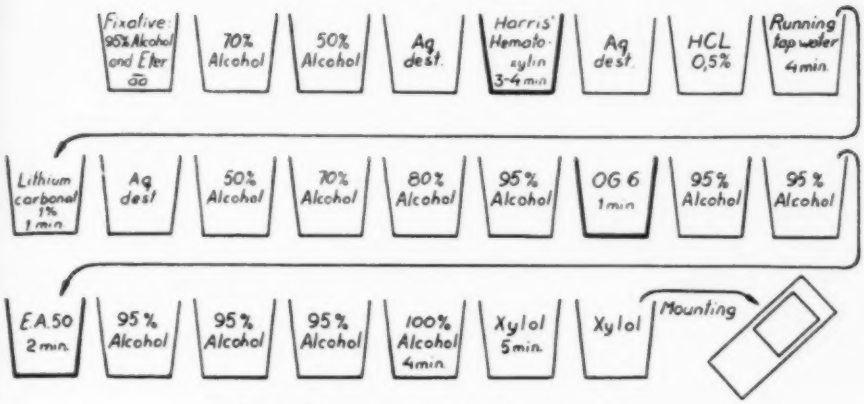

Fig. 1. PAPANICOLAOU staining procedure.

be expressed manually. The matter was then spread over the slide which was placed in the fixative. It is very important that the preparation be fixed immediately before it has time to dry, as secondary changes and less successful staining will otherwise be the result. The fixative used is that indicated by PAPANICOLAOU, consisting of equal parts of alcohol 96 % and ether. The preparations were fixed for at least one hour, but the staining ability will not decrease if they remain in the fixative for 48 to 72 hours.

Method of staining. The preparations were stained by PAPANICOLAOU's method (1954). This attempts to achieve the best possible staining of the nuclei, but at the same time the colouring of the cytoplasm must be so slight that the cells will be transparent and conceal each other as little as possible when they lie close in the preparation. After a great many experiments with various combinations of stain, PAPANICOLAOU arrived at a method in which he used HARRIS' hematoxylin for staining nuclei, and both orange G 6, and EA 36 or EA 50, the main ingredients of which are light green yellowish, Bismark brown, and eosin yellowish in different combinations for the cytoplasm.

By this method the nuclei are stained bluish-black, the acidophilic cells red to orange, and the basophilic cells blue to green; the erythrocytes become red, the leukocytic nuclei dark blue, and the cytoplasm light violet. The cytoplasm stains are dissolved in alcohol of a high percentage. Fig. 1 gives a full description of the staining procedure.

The method of staining is, as seen, somewhat circumstantial. Many attempts have therefore been made to achieve a more simple and rapid

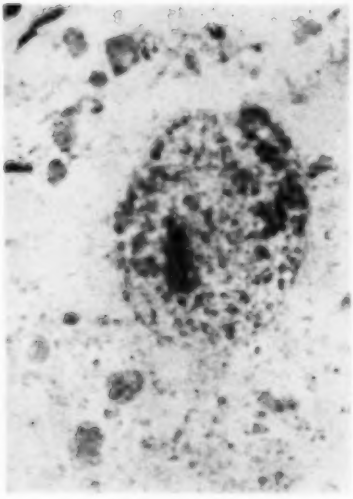

Fig. 2. Histiocytes of the "foamy cell" type. × 600.

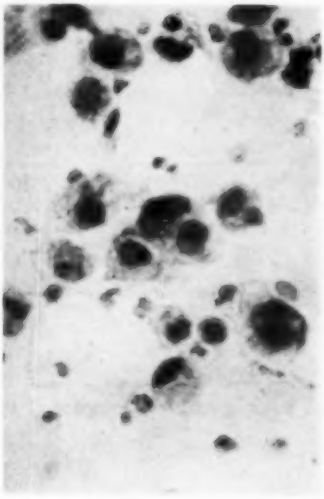

Fig. 3. Group of small histiocytes. × 600.

method. Several are available, but their use is rather limited. PAPANICOLAOU's method is superior for the cyto-morphologic diagnosis of cancer.

Cell pictures. My experience of cyto-morphologic studies of mammary discharge is in conformity with the account given in the introduction of, inter alios, PAPANICOLAOU. The preparations are generally easy to examine; they contain few cells, often red and sometimes white blood cells, the appearance of which does not deviate from the findings in cytologic examinations when using PAPANICOLAOU's method on secretions from other organs.

The so-called 'foamy cells' interpreted as histiocytes, frequently occur; their cytoplasm has a foamy appearance owing to a fine vacuolation. The nucleus is often eccentrically placed and is even and smooth with a chromatin pattern of a benign appearance (Fig. 2). Some histiocytes are smaller and have a comparatively large nucleus which often shows slightly greater activity; the cytoplasm is also vacuolized. These cells may appear singularly or in dense groups (Fig. 3). Furthermore, squamous cells of a typically benign appearance, probably from the nipple or the larger ducts may occur.

With papillomatosis in the milk ducts, groups of small cells are found; these are often rounded or oval and have a remarkably large nucleus, sometimes slightly hyperchromatic and showing a distinct nuclear mem-

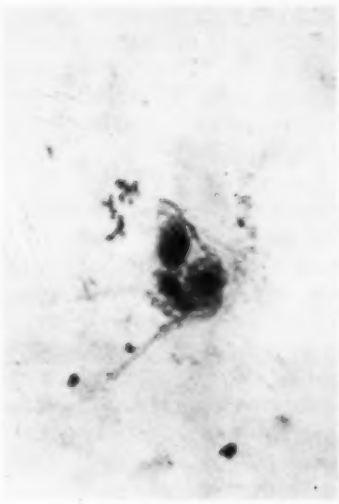

Fig. 4. Cells seen in cases of duct papilloma. × 600.

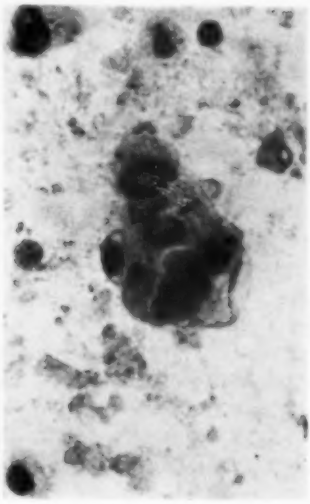

Fig. 5. Cluster of cancer cells. × 600.

brane. The nuclear pattern, however, is of the typically benign kind. These cells, in groups or en bloc, may possibly be the tip of a papilloma (Fig. 4). Appearances are sometimes noted in which the nuclei show a few, or several signs of malignancy, pointing to beginning malignant degeneration.

In cancer the picture is generally a very polymorphous one with an abundance of blood together with blood pigment and phagocytes. Furthermore, there are a varying number of tumour cells, showing variation in size and shape (Fig. 5). The diagnosis of cancer cells by PAPANICOLAOU's method is not based on any recently discovered characteristics of the carcinomatous epithelium, but depends on a great number of signs in cells exfoliated from malignant tumours; these signs have already been observed in histologic sections by various investigators. Neither are there distinct characteristics which decide whether a cell is carcinomatous, but there are many signs, although not specific, which however occur frequently and definitely in cells exfoliated from cancer tumours.

The criteria of malignancy are many and therefore only a brief survey will be given. (For further information see PAPANICOLAOU 1954.) Changes can be observed in both nucleus and cytoplasm as well as in the entire cell and the interrelationship between cells.

The most important criteria refer to the morphologic changes in the nucleus in which there is an unproportional enlargement so that the nucleo-cytoplasmic ratio is altered. An increase in the chromatin content is also typical, and the nucleus presents marked hyperchromatic appearance in addition to which the chromatin pattern in the nucleus is altered. The nucleoli also generally become enlarged and increase in number in the tumour cells. Multi-nucleation is also frequent and differs from the benign type as the nuclei are atypical. A marked thickening of the nuclear membranes is often found in the malignant cells, but may also occur in chronic infectious conditions. Certain alterations, pointing to malignancy appear in the cytoplasm, *e. g.* particular changes in stainability as well as the occurrence of granulations and phagocytosis in the cytoplasm. Atypical vacuolation of the cytoplasm is another sign of malignancy. Some changes in the entire cell also take place in cases of malignancy, as for instance, a greater enlargement of the cell than normal, or a deviation from the normal form, *e. g.* an extreme elongation or bizarre form or the formation of so-called 'tadpole cells'. Degenerative and necrobiotic changes are also frequently seen.

As regards the relation between different cells, anisokaryosis and anisocytosis occur as typical characteristics. The absence of distinct cell demarcations which allows the various cells to unite into an undifferentiated mass, is also a common sign of malignancy.

Finally, it may be said that none of the above-mentioned characteristics are specific per se, but rather that the most frequently occurring changes, such as disturbance in the nucleo-cytoplasmic ratio, hyperchromasia, multinucleation, anisocytosis, anisokaryosis, vacuolation, etc., must be taken together in order to obtain a reliable diagnosis of malignancy. An accurate knowledge of the normally exfoliated cells and extensive experience of their abnormal variations is necessary to use successfully the cytomorphologic technique for diagnosing cancer.

The aim of my investigation has been to explore the possibilities of diagnosing neoplastic processes which have caused nipple discharge. The cytologic findings have therefore been grouped in five different classes. Class I indicates normal finding without atypical or suggestive malignant cells; Class II includes cells with atypical appearances of different kinds; Class III covers atypias of such a high degree that there is strong suggestion of malignancy; in Class IV, findings of typical tumour cells have been included; Class V includes cytologic findings which have not been further classified owing to too few cells or to technically unsatisfactory reasons. The discharges taken from 39 cases have been divided up into these five groups in Table 4.

No attempts have been made to use the cytologic findings for diagnosing the pathologic process which may have been the cause of the dis-

Table 4

Cytologic classification

Class	Description	Number of cases
I	Normal cells, possibly only pus	16 + 1
II	Atypical cells occur	8
III	Cells, probably from malignant tissue	3
IV	Cells from malignant tissue	1
V	Technically unsatisfactory	10

charge. The interpretation has been limited to indicating the more or less probable neoplastic genesis, and the cytologic picture has consequently not been used in an attempt to diagnose, for example, cystic fibroadenomatosis. The various neoplastic processes which have been considered are cancer, papillomas, and atypical proliferations of the epithelium.

In 21 of the 39 patients, who were operated upon, the histologic findings were distributed as shown in Table 5.

Table 5

Histologic diagnosis of 21 patients operated on

(The patient is included in the earlier group in the table if there is more than one diagnosis)

Histologic diagnosis	Number of cases
Cancer	3
Papillomas	6
Atypical	2 (5)
Cyst. fibro-adenomatosis	8 (15)
Galactocele	1
Abscess	1

It is especially interesting to compare the cytologic finding with the pathologic diagnosis under different conditions. Among the patients showing a microscopically serous discharge the cytologic and pathologic diagnoses were distributed as shown in Table 6.

Table 6

12 patients with non-bloody discharge

(The patient is included in the earlier group in the table if there is more than one diagnosis)

A. Cytologic classification

Class	I	II	III	IV	V
Number of cases	6	1	1	0	4

B. Pathologic classification

Diagnosis	Cancer	Papillomas	Atypia	Cystic fibroadenoma	Abscess
Number of cases	1	0	1	4	1

Among 27 patients who had a microscopically bloody discharge the cytologic and pathologic diagnoses are distributed according to Table 7.

Table 7

27 patients with microscopically bloody discharge

(The patient is included in the earlier group in the table if there is more than one diagnosis)

A. Cytologic classification

Class	I	II	III	IV	V
Number of cases	11	7	2	1	6

B. Pathologic classification

Diagnosis	Cancer	Papillomas	Atypia	Cystic fibroadenoma	Abscess
Number of cases	2	6	1	5	1

In assessing the value of the cytologic examination in detecting neoplastic processes in the form of cancer, papillomas, or atypical proliferations of epithelium, a comparison of the cytologic and pathologic diagnoses in these conditions should be of interest. In Table 8, the cytologic results have been divided into positive and negative diagnoses and one group without any determined designation, *i. e.* cases not containing sufficient cells to make a definite diagnosis. Preparations which have contained atypical, or possible, or definite tumour cells have been regarded as positive. As is seen from the table, 2 of 3 patients with cancer had positive preparations; the third patient was regarded as negative at the first examination but a later study of the preparation showed that there was a group of atypical cells with dark, irregular nuclei. The cytoplasm was highly vacuolized with large deforming vacuoles. The picture may well tally with that seen in cells exfoliated from an adenocarcinoma, which was also the pathologic finding in this case. The patient has been considered as cytologically negative in the continued analysis.

Among the 6 patients having papillomatosis the discharge in one did not contain sufficient cells for diagnosis. Actually this preparation contained pure blood, which in itself suggested a neoplastic process. Furthermore, 1 patient with papillomatosis had a negative finding. The remaining 4, however, were positive. The 2 patients who had atypical proliferations of the epithelium without having cancer or papillomatosis,

were both positive. Among the 28 patients, in which no neoplastic process of the three above-mentioned types could be proved, 4 had a positive preparation. One of these patients, however, had received irradiation of the breast before the test, which probably contributed in producing atypical changes in the nucleus. One of the 4 patients had a cystic fibroadenomatosis which was highly infected and contained pus, and one patient had an ordinary cystic fibroadenomatosis. One of the 4 patients has not yet been operated on.

Table 8

Correlation between the cytologic and histologic diagnoses

Cytology	Pathologic diagnosis				
	Cancer	Papillomas	Atypia	Non-neoplastic process	Total
No cells	—	1***	—	9	10
Negative	1*	1	—	15	17
Positive	2	4	2	4**	12
Total	3	6	2	28	39

* Positive when re-checked.
** One patient received irradiation
" " had an infected cystic fibroadenomatosis
" " " a cystic fibroadenomatosis
" " non-operated.
*** Pure blood.

Of the 11 patients, who in the histologic examination showed some kind of neoplastic process, 8 or 73 per cent have been diagnosed by means of the cytologic examination. Three of the 11 neoplastic processes were not possible to diagnose cytologically, or 27 per cent calculated among the cases of neoplasms. Among the 27 non-positive cytologic diagnoses, 3 or 11 per cent were 'false negative'. Four of the 28 patients who pathologically or clinically had no neoplastic processes were positive, *i. e.* there were 14 per cent 'false positives'.

SUMMARY

The frequency of bleeding from the nipple in a cancer of the breast material is stated to vary between 1 and 5 per cent. The frequency of mammary cancer in patients with such bleeding is reported to be 36 to 50 per cent. Intraductally growing papillomas causing bleeding from the nipple are given as 11 to 44 per cent.

Thirty-nine patients with nipple discharge were examined cytologically according to PAPANICOLAOU's technique. The method and the findings are discussed. The cytologic examination seems to offer an additional diagnostic possibility in cases of discharge from the nipple. The results are encouraging and the method appears worth trying on a larger case material.

ZUSAMMENFASSUNG

Es wird angegeben, dass die Frekvenz von Mamillenblutungen beim Mammakarzinom zwischen 1 und 5 % schwankt. Die Häufigkeit eines Mammakarzinomes bei Patienten mit blutender Mamma wird mit 36 bis 50 % berichtet. Intrakanalikulär wachsende Papillome als Ursache einer blutenden Mamma werden mit 11 bis 40 % angegeben.

Neununddreissig Patientinnen mit Mamillensekretion sind zytologisch mit der von PAPANICOLAOU angegebenen Technik untersucht worden. Die Methode und die Befunde werden besprochen. Die zytologischen Untersuchungen scheinen eine zusätzliche diagnostische Möglichkeit in Fällen mit Sekretion von der Mamille zu bieten. Die Ergebnisse sind ermutigend und es scheint der Mühe wert zu sein, die Methode in grösserem Umfange zu benutzen.

RÉSUMÉ

On estime que la fréquence du saignement du mamelon dans le cancer du sein varie entre 1 et 5 pour cent. La fréquence du cancer du sein, chez les malades présentant un saignement du mamelon, est évaluée à 36 à 50 pour cent. Les papillomes intracanaliculaires donnant un saignement du mamelon iraient de 11 à 44 pour cent.

Trente-neuf malades ayant un écoulement mamelonnaire ont eu un examen cytologique suivant la technique de PAPANICOLAOU. L'auteur examine cette méthode et ses résultats. L'examen cytologique paraît offrir une possibilité diagnostique supplémentaire dans les cas d'écoulement du mamelon. Les résultats sont encourageants et cette méthode paraît mériter d'être mise à l'épreuve sur une plus grande échelle.

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INDEX

The temporal horn: its development, normal variations and changes associated with non-expanding epileptogenic lesions of the temporal lobe. By *John M. Van Buren, Maitland Baldwin* and *Ellsworth C. Alvord Jr* 703

Cholecystography with the sodium salt of iopanoic acid. By *Rome Peterhoff* 719

Cholegraphic demonstration of cystic duct obstruction. By *P. Lörinc* and *T. Herczeg* 723

Three cases of eosinophilic granuloma of the pelvis in children. By *Lorentz Nitter*. 731

Calibration of the portable Swedish free-air chamber equipment at the U.S. National Bureau of Standards. By *R. Thoraeus* and *H. O. Wyckoff*. . . 741

An intercomparison of the roentgen standards of Great Britain and U.S.A. By *G. H. Aston* and *F. H. Attix* 747

Cytologic studies of nipple discharge. By *Olle Kjellgren* 753

Books received. 768

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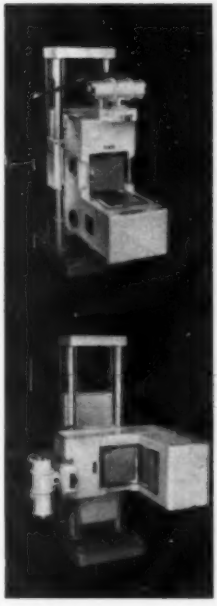

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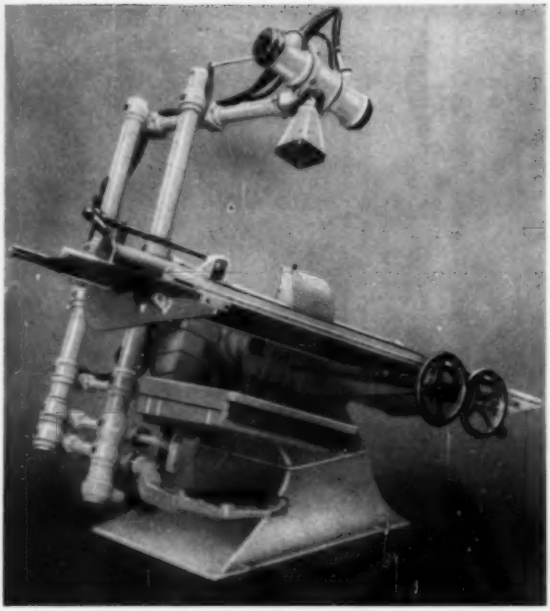

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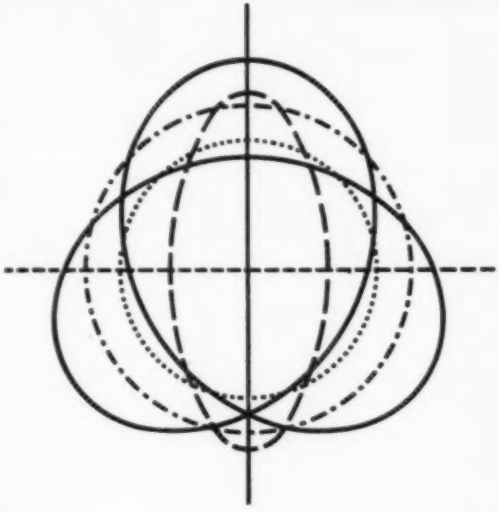

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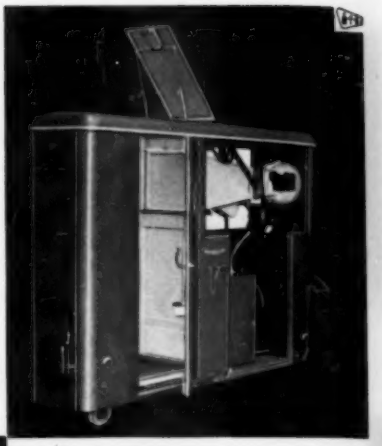

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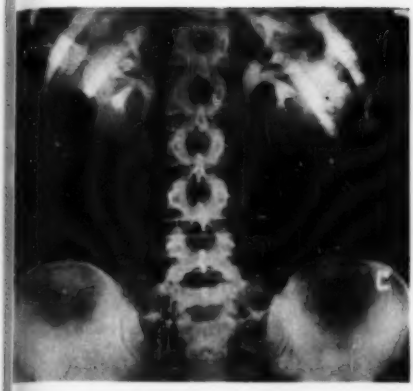

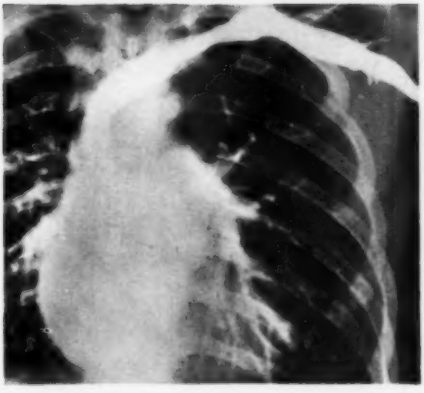

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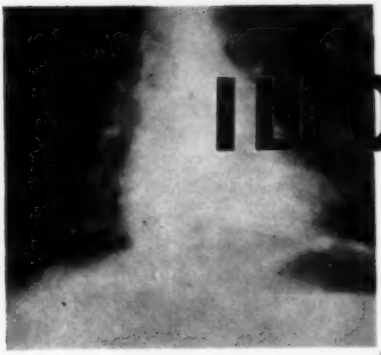

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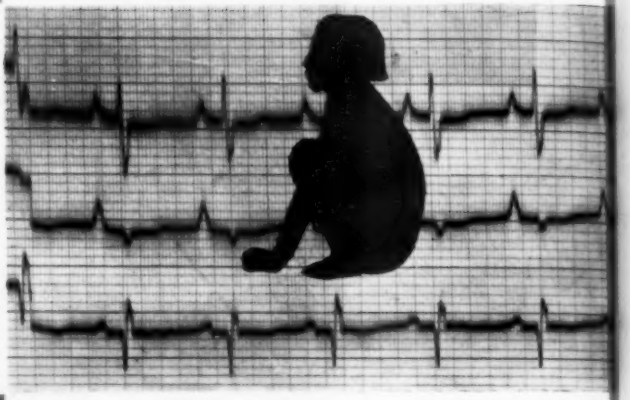

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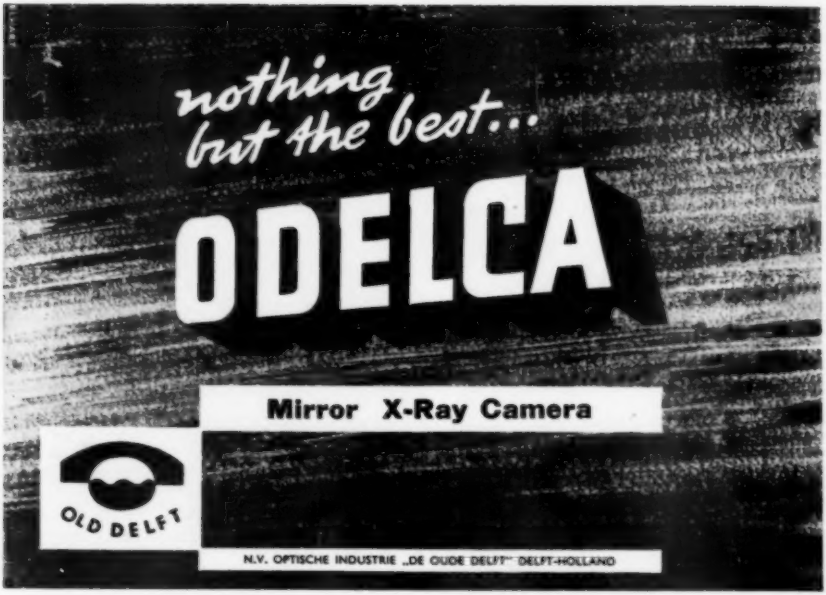

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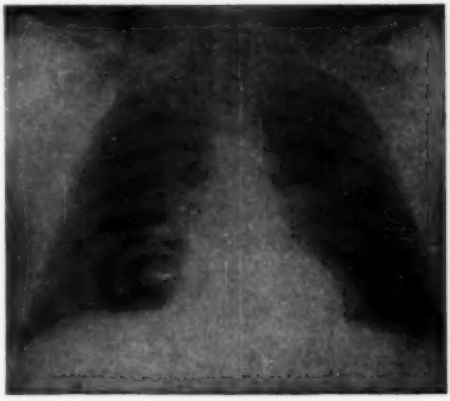

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